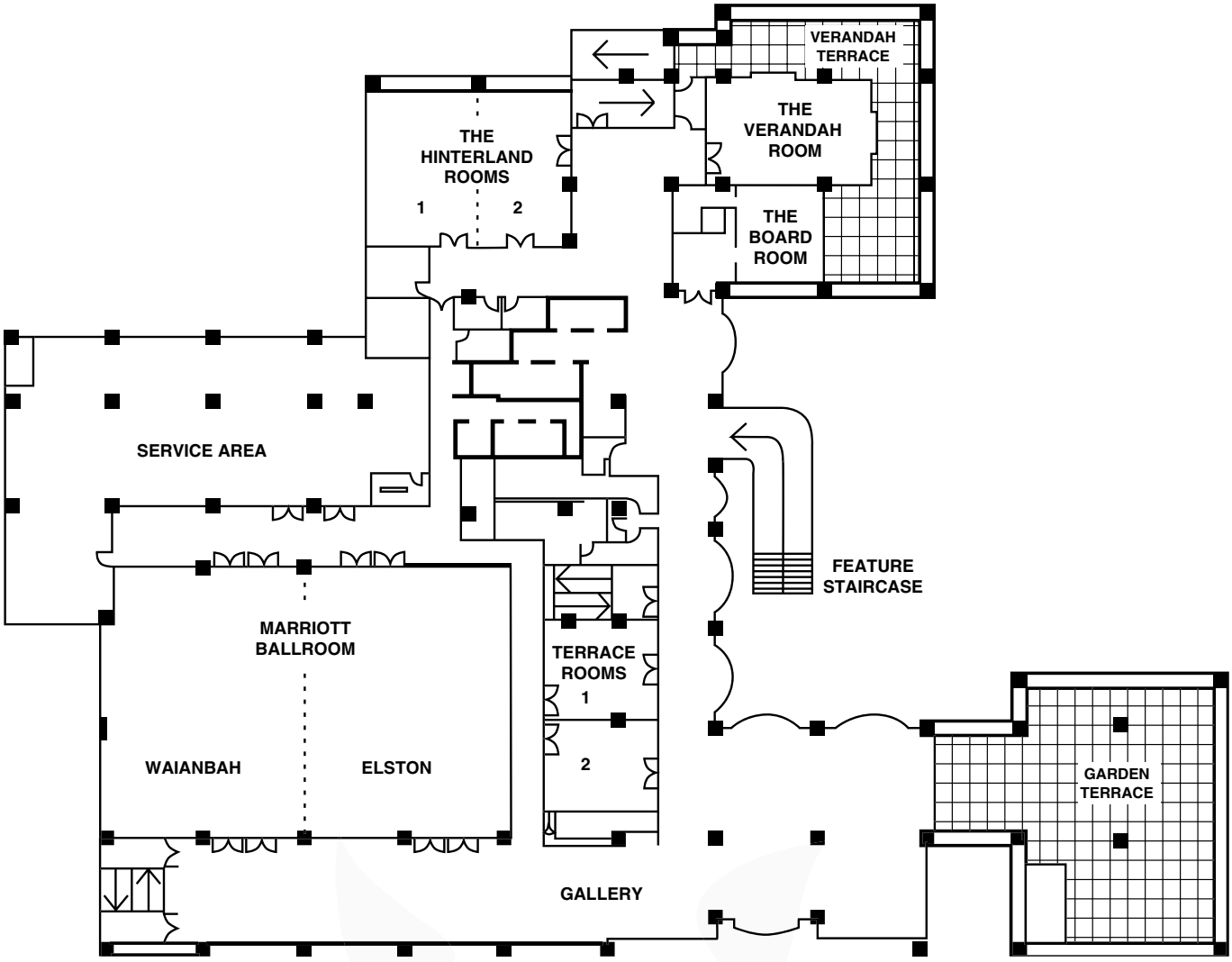
HANDBOOK AND ABSTRACTS

Fifth Scientific Meeting of the Australasian Society for Breast Disease

22-24 SEPTEMBER 2005

SURFERS PARADISE MARRIOTT RESORT

Conference Level



CONTENTS

SECTION I

Welcome 4

Australasian Society for Breast Disease Executive Committee 4

Sponsors 6

Trade Exhibition 7

Useful Information 7

Social Program 8

Keynote Speakers 9

Faculty 9

Poster Presentation 11

Scientific Program 12

SECTION II

Abstracts 17

SECTION 1
Handbook

WELCOME

On behalf of the Executive Committee, I welcome you to the Fifth Scientific Meeting of the Australasian Society for Breast Disease.

This Meeting is designed to help health care professionals advance their knowledge of the latest techniques of investigation and management of breast cancer. Breast cancer screening in Australia will be reviewed as well as survivorship in breast cancer and patient outcomes. The Meeting also provides an excellent opportunity for professional and social interaction between delegates from the various disciplines.

I wish to thank our sponsors AstraZeneca Oncology, Novartis Oncology, Toshiba and Roche Products, as well as all the exhibitors for their tremendous support. It would not be possible to hold this Scientific Meeting without their support.

To help us in our future planning, we would greatly appreciate it if you took the time to complete the brief questionnaire provided in your satchel. Please drop the completed questionnaire into the box placed in the Meeting Office.

Enjoy the Meeting!

Warwick Lee
President

AUSTRALASIAN SOCIETY FOR BREAST DISEASE EXECUTIVE COMMITTEE

Warwick Lee	Radiologist, President
Geoffrey Beadle	Medical Oncologist, Secretary/Treasurer
Natacha Borecky (co-opted)	Radiologist
Marie-Frances Burke	Radiation Oncologist
Jennet Harvey	Pathologist
Nehmat Houssami	Breast Physician / Clinical Epidemiologist
Michael Izard	Radiation Oncologist
Jack Jellins (co-opted)	Scientist
James Kollias	Surgeon
Lynne Mann (co-opted)	Surgeon
Veronica Macauley-Cross (co-opted)	BCNA Representative
Margaret Pooley (co-opted)	Surgeon
Wendy Raymond (co-opted)	Pathologist
Mary Rickard	Radiologist
Robin Stuart-Harris (co-opted)	Medical Oncologist
Solei Gibbs	Executive Officer

Previous Executive Committee Members

Michael Bilous	Pathologist
John Boyages	Radiation Oncologist
Colin Furnival	Surgeon
Michael Green	Medical Oncologist
Cherrell Hirst	Breast Physician
Elspeth Humphries (co-opted)	BCNA Representative
William McLeay	Surgeon

CONTACT DETAILS

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Website: www.asbd.org.au

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In Australia, AstraZeneca is the fourth largest pharmaceutical company with annual sales of approximately $600 million.

Employing more than 1,000 people across sales, manufacturing and the head office division, AstraZeneca provides healthcare solutions across seven major therapeutic areas including cardiovascular, neuroscience, gastrointestinal, infection, oncology, pain control and anaesthesia and respiratory medicines.

Every day more than 1.5 million Australians benefit from our medicines. The manufacturing facility completed the final stage of its $19.35million extension in 2004. Exporting pharmaceutical products from its Sydney plant to more than 30 countries around the world including Europe, Asia, New Zealand and Japan, AstraZeneca's export sales exceeded $137 million in 2004.

AstraZeneca is a leading global research and development organisation with one of the best pipelines in the pharmaceutical industry.

Globally we spend AUD$18million each working day on R&D with more than 12,000 researchers dedicated to the discovery and development of innovative new medicines that meet the needs of patients worldwide.

On a national level, AstraZeneca participates in more than 40 clinical trials across 200 Australian centres. In 2004, in excess of AUD$20million was invested in Australian clinical research projects.

AstraZeneca continues its tradition of research excellence and innovation in Oncology that led to the development of its current anti-cancer therapies including 'Arimidex, 'Cosudex', 'Iressa', 'Nolvadex', 'Tomudex' and 'Zoladex' as well as a range of novel targeted products such as anti-proliferative, anti-angiogenic, vascular targeting and anti-invasive agents. AstraZeneca is also harnessing rational drug design technologies to develop new compounds that offer advantages over current cytotoxic and hormonal treatment options. The company has over 20 different anti-cancer projects in research and development.

AstraZeneca is proud to be supporting the Fifth Scientific Meeting of the Australasian Society for Breast Disease.

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At Novartis Oncology we strive to provide a broad range of innovative therapies that change the way patients live with cancer. In Australia, Novartis Oncology is dedicated to bringing these novel therapies to the market so that patients and health care providers are able to access treatments that will enhance patients' lives.

At Novartis Oncology, the pursuit for excellence in research, clinical trial development and local initiatives is the commitment we make to health care providers and patients.

The Novartis representatives present at this meeting would be happy to answer any questions related to Novartis Oncology products.

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Ph: 02 9805 3555
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12. & 13.	Sanofi-Aventis
14. & 15.	AstraZeneca Oncology
16.	Philips Medical Systems Australasia
17.	Focus Medical Technologies
18.	Sectra Pty Ltd
19.	Siemens Ltd – Medical Solutions
20.	Eli Lilly Australia

Venue

Surfers Paradise Marriott Resort
158 Ferny Avenue
Surfers Paradise Qld 4217
Australia

Telephone: (07) 5592 9800 (from overseas: +61 7 5592 9800)
Facsimile: (07) 5592 9888 (from overseas: +61 7 5592 9888)

Meeting Office

The Meeting Office is located in Terrace Room 1 on level 2 and it will be open during the following times:

Thursday 22 September 2005	1400-2000 hours
Friday 23 September 2005	0700-1730 hours
Saturday 24 September 2005	0730-1700 hours

Speakers' Audiovisual Testing Room

The Speakers' Audiovisual Testing Room is located in Terrace Room 11, adjacent to the Meeting Office. The opening hours are:

Thursday 22 September 2005	1600-1900 hours
Friday 23 September 2005	0730-1600 hours
Saturday 24 September 2005	0730-1300 hours

Namebadges

Please wear your namebadge at all times. It is your admission pass to sessions and morning and afternoon teas. If you misplace your namebadge, please contact the Meeting Office.

Namebadges are colour coded as follows:

ASBD Executive Committee member	Blue
Speaker	Light blue
Others	White

Tickets

Attendance at workshops and social functions is by ticket only. Tickets are enclosed in your registration envelope with your namebadge, according to your attendance indication on the registration form. If you misplace any tickets or do not have tickets to the activities you wish to attend, please contact the Meeting Office.

Special Diets

If you have made a special dietary request, please identify yourself to serving staff at functions.

Messages

A message board is located near the Meeting Office. Please advise potential callers to contact the Surfers Paradise Marriott Resort (see details above) and ask for the Australasian Society for Breast Disease Meeting Office. Please check the board for messages as personal delivery of messages cannot be guaranteed.

Dress

Smart casual attire is appropriate for Meeting sessions and social activities, including the Meeting dinner (although you are welcome to 'dress up' for the masquerade dinner).

Lunches

Lunches will be served in the Garden Terrace room and the Trade Exhibition area. Lunch service is by ticket only. Please ensure you have the correct tickets. Additional tickets are available at $33 per person.

Welcome Drinks

Sponsored by AstraZeneca Oncology

Thursday 22 September 2005, 1800-1900 hours

Join your fellow delegates for a relaxed drink by the pool area or, in case of the weather not being favourable, in the Garden Terrace room. Included for fulltime delegates and registered partners. Additional tickets cost $25 per person.

Networking Drinks

Sponsored by Novartis Oncology

Friday 23 September 2005, 1730-1900 hours

Following the last session for the day, take the opportunity to meet your colleagues and trade representatives for drinks in the Trade Exhibition area. Included for fulltime and Friday delegates and registered partners only.

Meeting Dinner

Sponsored by AstraZeneca Oncology

Saturday 24 September 2005, 1830-2300 hours

This year, we will conclude the Meeting with the magic of a masquerade dinner party. The evening will start with pre dinner drinks in the Garden Terrace, followed by a fine dinner, drinks and music in the Marriott Ballroom. While it may take a while for everyone to recognise who's who, wearing the mask is **compulsory** for admission to the festivities!

Included for full time delegates and registered partners. Additional tickets at $99 per person must be purchased by Thursday 22 September 2005 from the Meeting Office.

Optional Social Activities

For information about and bookings for leisure activities such as golf, fishing and cruises, please contact the Tour Desk at the Marriott during your stay.

The Annual General Meeting of the Australasian Society for Breast Disease will be held in the Verandah Room at 0730 hours on Saturday 22 September 2005. Breakfast will be served during the Meeting. Please reconfirm you attendance/nonattendance upon registration. Admission is free to members only.

CONSUMER WORKSHOP

Australasian Society for Breast Disease, in partnership with the Breast Cancer Network of Australia, will hold its second Consumer Workshop on Saturday 24 September 2005, in the Hinterland Rooms. The goals of the workshop are to bring women with a personal experience of breast cancer to a forum that will examine the basis of trust in the patient doctor relationship. The workshop will also include a summary of the highlights of the Fifth Scientific Meeting. Following the morning break, an invitation has been extended to the participants to join the Meeting delegates in the scientific sessions. The Consumer Workshop will be facilitated by Dr Geoffrey Beadle, Ms Veronica Macaulay-Cross and Dr Margaret Pooley.

BREAST PHYSICIANS

The Annual General Meeting of the Australasian Society of Breast Physicians will be held at 1830 hrs on Friday 23 September 2005, in Hinterland Room 1.

Hiram S Cody III MD

Hiram "Chip" Cody is the current Professor of Clinical Surgery at the Weill Medical College of Cornell University and Attending Surgeon on the Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA. Professor Cody is the Principal Investigator of the sentinel node program at the MSKCC and this has been the main focus of his clinical research over the last 10 years. He is currently a member of the ASCO Lymphatic Mapping Working Group and has over 120 scientific publications, book chapters and monographs in high profile scientific medical and surgical journals.

Shahla Masood MD

Shahla Masood currently holds the positions of Professor and Associate Chair Department of Pathology at University of Florida and Chief of Pathology and Laboratory Medicine at Shands, Jacksonville, Florida, USA. An internationally recognized expert in breast cancer diagnosis and prognosis, Professor Masood has fostered the concept of an integrated multidisciplinary approach in breast cancer care, research and education. She is the founder and Editor-in-Chief of *The Breast Journal,* and the founder and the Past President of the "International Society of Breast Pathology".

Nicole McCarthy MBBS, MHSc, FRACP

Sponsored by AstraZeneca Oncology

Nicole McCarthy is a Senior Lecturer in Medical Oncology at the University of Auckland, New Zealand, and is the recipient of the Breast Cancer Research Trust Fellowship Grant. Her current research interests include: primary chemotherapy for locally advanced breast cancer; clinical trials incorporating new anticancer agents; and breast cancer advocacy. Dr McCarthy is a member of American Society of Clinical Oncology, Medical Oncology Group of Australia, Australia and New Zealand Breast Cancer Trials Group and the New Zealand Cooperative Oncology Group.

A Thomas Stavros MD

Sponsored by Toshiba

Thomas Stavros has been the Chief of Ultrasound and non-invasive vascular services with Radiology Imaging Associates, Medical Imaging of Colorado, and Swedish Medical Center, Denver, Colorado, USA since 1979. Professor Stavros has been involved in mammography since joining RIA in 1976, and has been actively involved in the development of high-frequency hand-held breast ultrasound since 1981. Professor Stavros is an honorary fellow of the Royal Australian and New Zealand College of Radiology, where he was the Baker Professor in 1999.

FACULTY

Dr Geoffrey Beadle MBBS, FRACP, FRANZCR

Geoffrey Beadle trained in medical oncology and radiation oncology at the Peter MacCallum Cancer Institute and undertook post qualification training in radiation oncology at the Joint Center for Radiation Therapy, Harvard Medical School, Boston. After returning to Brisbane, he worked at the Queensland Radium Institute in radiation oncology before moving to the Wesley Medical Centre where he has practiced in medical oncology for the past 15 years. He currently holds a part-time appointment at the Queensland Institute of Medical Research as head of the Translational Research Laboratory.

Professor James F Bishop MD, MMed, MBBS, FRACP, FRCPA

James Bishop is the Chief Cancer Officer and Chief Executive Officer at the Cancer Institute NSW, and Professor of Cancer Medicine at the University of Sydney.

Dr Marie-Frances Burke MBBS, FRACR

Marie Burke graduated in medicine from the University of Queensland in 1982. Since 1989, she has been a Fellow of the Royal Australasian College of Radiologists, having done her training in radiation oncology at the Queensland Radium Institute, in Brisbane. She is currently in practice as a Radiation Oncologist at the Wesley Cancer Care Centre, Brisbane. Dr Burke's major interests are in breast and gynaecologic cancers. She is a member of the Executive Committee for the Australasian Society for Breast Disease.

Dr Jennifer N Cawson MBBS, FRACR, MPH, MD (Graduand)

Jennifer Cawson is the founder and convener of the BIG group of the RANZCR. She is currently Director of St Vincent's BreastScreen and is active on committees for the RANZCR, BreastScreen and other national and state bodies. Dr Cawson's current research interests include breast density and its effect on the sensitivity and specifity of mammography, investigation of the links between breast density and genetic factors comparing dizygotic and monozygotic twins, the accuracy of computer aided diagnosis, the association of radial scar of the breast with breast cancer and the sonographic and mammographic findings of radial scar. She has a strong interest in education and training and offers breast Imaging Fellowships to young local and ASEAN radiologists.

Dr Glenn Francis MBBS, FRCPA, MBA

Glenn Francis is a graduate of the University of Queensland who has trained in general pathology. He subsequently worked for Queensland Medical Laboratory until early 2005. He is currently deputy director of laboratory services, Queensland Health Pathology Service and Director of Pathology Princess Alexandra Hospital, Brisbane. Other appointments include Assessor, National Association of Testing Authorities, HER 2 Advisory Board to Roche, Royal College of Pathologists of Australasia (RCPA) Board of Education, and RCPA Quality Assurance and Education Committees. His research activities include prognostic biomarkers in breast cancer, neural network applications in pathology, and in-situ hybridization.

A/Professor Jennet Harvey MBBS, FRCPA

Jennet Harvey is Associate Professor at The University of Western Australia and Head of Pathology. She is a consultant pathologist working at the PathWest Laboratory Medicine WA, with a particular interest in breast pathology. In addition to currently serving on the WA State Committee of the Royal College of Pathologists of Australasia, she is a member of a number of University and Faculty committees and the Board of Basic Surgical Training of the Royal Australian College of Surgeons. Professor Harvey is also on the Executive Committee of the Australasian Society for Breast Disease and a Councillor, Australian Council on Smoking and Health.

Dr Nehmat Houssami MBBS (Hons), MPH, M Ed, FAFPHM (RACP), FASBP, PhD

Nehmat Houssami is a Breast Physician and a Public Health Physician and has worked in multidisciplinary breast services for the past 15 years. She is an established researcher in applied clinical epidemiology focusing on breast diagnosis, imaging and screening. She is Associate Clinical Director of the NSW Breast Cancer Institute, VMO at the Royal Hospital for Women, and Honorary Senior Lecturer with the School of Public Health (Sydney University). She has published extensively in the international literature, and is a research associate with Florence's Centro per lo Studio e la Prevenzione Oncologica. She is the current Specialty Editor for 'Imaging, Screening & Early Diagnosis' with *The Breast* journal.

Dr Michael Izard MBBS (Lon), FRANZCR

Michael Izard works at the Mater Hospital in Sydney, as a partner in private practice. He trained in medicine at The Middlesex Hospital in London, coming out to Australia shortly after. His radiation oncology training was at St Vincent's and Westmead Hospitals in Sydney, with a year as Clinical Fellow at Princess Margaret Hospital in Toronto, Canada. Dr Izard is involved with the Multi-Disciplinary Breast Clinic held at the Mater.

Mr James Kollias MBBS, FRACS, MD

James Kollias is a specialist breast surgeon at the Royal Adelaide Hospital, St Andrews Breast Clinic and BreastScreen South Australia. He is a member of the Executive of Royal Australian College of Surgeons (RACS) Breast Section, RACS Breast Audit Executive subcommittee, and the Clinical Director of the RACS National Breast Cancer Audit. Mr Kollias' special interests include breast training and oncoplastic breast surgery.

Dr Warwick Lee MBBS, BSc(Med), FRANZCR, DDU

Warwick Lee is a radiologist in private practice in Bowral, NSW and a Visiting Radiologist with BreastScreen – NSW Greater Western Sydney. He has been involved with breast cancer screening since 1988 when he was part of the pilot mammography screening programme, The Central Sydney Area Health Service Breast X-ray Programme.

Ms Veronica Macaulay-Cross DipTeach, B Ed

Veronica Macaulay-Cross is one of the two Queensland state representatives for Breast Cancer Network Australia (BCNA). She was a secondary school teacher for over 20 years and served on various committees including the Executive Committee of the Queensland Teachers' Union. In 1996, aged 40 years, Ms Macaulay-Cross was diagnosed with breast cancer; and again in 1999 with metastatic breast cancer. She has worked on committees with Queensland Health, Queensland Cancer Fund, the National Breast Cancer Centre and the National Breast Cancer Foundation. In 2003, she represented BCNA at a consumer forum in Copenhagen and attended ECCO. Ms Macaulay-Cross presented a workshop at the 2004 National Breast Care Nurses Conference, and a poster at the 2004 National Oncology Nurses Conference.

Dr Treasure McGuire B Pharm, B Sc, PostgradDipClinHospPharm, PhD

Treasure McGuire is a drug information pharmacist and educator. She recently completed her PhD on what motivates consumers to medicines information seek. In her Mater role, she manages the Pharmacy's Academic Practice Unit and three national medicines call centres. As a Conjoint Lecturer in the School of Pharmacy, Dr McGuire teaches in the *Quality Use of Medicines* stream on medication safety and *Quality Use of Medicines* in communicable diseases, women's and men's health, and complementary medicines.

Dr Kerry McMahon MBBS, FRANZCR

Kerry McMahon is a radiologist with Queensland X-Ray in Brisbane where she has a special interest in women's imaging. This includes all aspects of breast imaging including Breast MRI, obstetric and gynaecologic ultrasound and bone mineral densitometry. She is a graduate from the University of Queensland, completing her radiology training at the Royal Brisbane Hospital and a fellowship year in Women's Imaging at the Edinburgh Royal Infirmary. She has been in private practice with Qld X-Ray since 1999, and is a visiting consultant to BreastScreen Queensland. More recently, Dr McMahon has also become associated with the University of Queensland, in developing further research into Dynamic Breast MRI, and mathematical models of enhancement kinetics.

Ms Jennifer Muller Dip Rad (Diag), Grad Dip Hlth Ed, M Environ. and Community Health

Jennifer Muller is Director of Queensland Health's Cancer Screening Services Unit, where she has been responsible for population screening and early detection programs that have significantly reduced the impact of cancer in our community. She helped to establish the National Cervical Screening program and BreastScreen Australia Program, which she also implemented in Queensland. Ms Muller pioneered the Rural and Remote Women's Health Program; the Mobile Women's Health Nurse Service and led the development of the Queensland Indigenous Women's Cervical Screening Strategy. To complement these programs, she developed and implemented Queensland Health's Pap Smear Registry and the BreastScreen Queensland Registry database systems. Currently, Ms Muller is working to develop the state component of the National Bowel Cancer Screening Program.

Dr Susan C Pendlebury MBBS, FRANZCR

Susan Pendlebury is a senior staff specialist in Radiation Oncology at Royal Prince Alfred Hospital. She has a specialist Breast cancer practice and works clinically within both the public and private sectors. She has been involved with the administration of the Sydney Breast Cancer Institute, as its Director during 2004. Dr Pendlebury has extensive experience with guideline development both within her own institution and nationally for the National Breast Cancer Centre.

A/Professor Mary Rickard MBBS, BSc (Med)(Hons), MPH, FRANZCR, DDU

Mary Rickard has been involved in mammography screening for breast cancer since her appointment in 1987 as director of a pilot project, now part of BreastScreen Australia. As a radiologist, she has taken a keen interest in quality assurance in mammography and breast ultrasound technique and interpretation, and in correlative diagnosis of breast disease. Professor Rickard, currently appointed as State Radiologist for BreastScreen NSW, frequently lectures on breast disease diagnosis in Australia and overseas, and is involved in activities related to breast disease for the College of Radiologists (RANZCR), the National Breast Cancer Centre (NBCC), the International Breast Ultrasound School (IBUS), the Australasian Society for Breast Disease (ASBD) and other bodies.

Professor David Roder DDSc, MPH, AM

David Roder heads the Centre for Cancer Control Research at The Cancer Council South Australia (SA) and is a Professorial Fellow at Flinders University. He directed the SA Epidemiology Branch between 1980 and 2001, which included the development of population and hospital cancer registries. He was made a Member of the Order of Australia in 2000 for contributions to cancer registration and epidemiology. Professor Roder has authored approximately 130 peer-reviewed journal publications and many technical reports. He has been a member of the State Accreditation Committee of BreastScreen SA and, since mid-1990s, the National Quality Management Committee of BreastScreen Australia.

Dr Martin Stockler MBBS, MSc, FRACP

Martin Stockler is Senior Lecturer in the Department of Medicine and School of Public Health, University of Sydney, Consultant Medical Oncologist at the Sydney Cancer Centre, Co-Director of Cancer Trials at the Australian NHMRC Clinical Trials Centre and Director of Cancer Trials at The Cancer Council of NSW. After medical oncology specialty training at the Royal Prince Alfred Hospital, Dr Stockler spent three years in Canada at the Princess Margaret Hospital and the University of Toronto completing a clinical fellowship in oncology and a Masters in Clinical Epidemiology. His special interests are: incorporating assessment of quality of life and preferences in research and practice; clinical trials, meta-analysis, quantitative methods; evidence-based medicine in clinical practice and medical education; patient-doctor communication; and genito-urinary, breast and advanced cancer.

A/Professor Robin Stuart-Harris MBBS, MD, FRCP, FRACP

Robin Stuart-Harris trained in medical oncology and palliative care at the Royal Marsden Hospital London but migrated to Australia in 1987. In February 1998, he took up the appointment of Senior Staff Specialist in Medical Oncology at the Canberra Hospital and Associate Professor of Medical Oncology at the Australian National University. In August 2004, he was appointed as Director of the Capital Region Cancer Service. Professor Stuart-Harris has particular interests in the management of both early and advanced breast cancer and the psychosocial aspects of cancer.

Dr Jane Turner MBBS, FRANZCP

Jane Turner is a Senior Lecturer in Psychiatry at the University of Queensland, with responsibility for teaching medical students in the MBBS program. Her clinical work and research interests include wellness following cancer treatment, and issues facing patients and their families coping with advanced cancer. Dr Turner is involved in communication skills training and in the development and dissemination of Clinical Practice Guidelines for the management of women with breast cancer and psychosocial care of adults with cancer.

Dr Helen Zorbas MBBS, FASBP

Helen Zorbas is Director of the National Breast Cancer Centre (NBCC). She has been responsible for directing a number of key national projects and programs in evidence-based practice, clinical guidelines, monitoring, service improvement and psychosocial support to improve cancer care. Her position is also responsible for ensuring clinical integrity, accuracy, consistency and relevance of the NBCC's clinical and public information resources.
Dr Zorbas' current appointments include: member of the Health Advisory Committee of the NHMRC; member, NHMRC Hormone Replacement Therapy Working Party; member, Commonwealth Government's National Cancer Strategies Group; member, Australian Screening Advisory Committee (ASAC); Chair, ASAC Quality Improvement and Workforce Working Party; Chair, NHMRC Microwave Cancer Review Committee; and, member, Cancer Screen NSW Advisory Committee.

PRESENTERS – PROFFERED PAPERS

Dr Toni J Jones PhD, MAPS

Neuropsychologist – Study Coordinator, Queensland Institute of Medical Research / Wesley Research Institute, Brisbane, Queensland

Dr Nirmala Pathmanathan BSc(Med), MBBS, FRCPA

Staff Specialist, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Sydney, New South Wales

Dr Emma Pun MBBS, FRANZCR

Radiology Fellow, Peter MacCallum Cancer Institute, Melbourne, Victoria

Dr Patsy Soon MBBS, FRACS

Research Fellow, Kolling Institute, Royal North Shore Hospital, Sydney, New South Wales

Mr Neil R Wetzig MBBS, FRACS, FRCS (Eng)

Senior Visiting Surgeon, Princess Alexandra Hospital (and The Wesley Hospital and Mater Private Hospital), Brisbane, Queensland (on behalf of the) RACS SNAC Group

Dr Helen Zorbas MBBS, FASBP

Director, National Breast Cancer Centre, Sydney, New South Wales

The Poster Presentation will be located outside the main Meeting session room for the duration of the Meeting.

VENUES

Thursday 22 September 2005

1400-2000hrs	Registration Venue: Terrace Room I
1600-1900	Speakers' audiovisual testing Venue: Terrace Room II
1800-1900	Welcome drinks Venue: Pool side
	Workshop: *Case presentations – Radiology / Pathology / Clinical Correlation* Venue: Verandah Room
	Workshop: *Sentinel Node / Axilla management* Venue: Hinterland Room I
	Workshop: *Sonographic evaluation of breast cysts that are not simple* Venue: Ballroom
	Workshop: *Effectively communicating prognosis* Venue: Hinterland Room II

Friday 23 September 2005

0730-1730hrs	Registration Venue: Terrace Room I
0730-1600	Speakers' audiovisual testing Venue: Terrace Room II
1830-1930	Australasian Society of Breast Physicians Annual General Meeting Venue: Hinterland 1

Saturday 24 September 2005

0730-1700hrs	Registration Venue: Terrace Room I
0730-0845	Australasian Society for Breast Disease Annual General Meeting Venue: Verandah Room
0730-1300	Speakers' audiovisual testing Venue: Terrace Room II
0900-1030	Consumer workshop Venue: Hinterland Rooms
1930-2300	Meeting dinner Venue: Garden Terrace / Ballroom

The venue for all scientific program plenary sessions is the Marriott Ballroom.

Thursday 22 September 2005

1400 – 2000	Registration
1800 – 1900	Welcome Drinks *Sponsored by AstraZeneca Oncology*
1900 – 2030	**Workshops** (concurrent)

1. Case presentations – Radiology / Pathology / Clinical Correlation
- Shahla Masood and Jennifer Cawson

2. Sentinel Node / Axilla management
- Hiram Cody
Sponsored by Novartis Oncology

3. Sonographic assessment of breast cysts that are not simple
- Thomas Stavros
Sponsored by Toshiba

4. Effectively communicating prognosis
- Jane Turner
Sponsored by National Breast Cancer Centre

Friday 23 September 2005

0730 – 0900	Registration
0900 – 1030	**Session 1 – Opening Session** *Sponsored by AstraZeneca Oncology* Chair: Warwick Lee ***Opening Remarks, Welcome:*** Warwick Lee ***Keynote Address: The axilla*** Hiram Cody ***Keynote Address: Borderline breast lesions*** Shahla Masood ***Keynote Address: Neoadjuvant systemic treatment for early breast cancer*** Nicole McCarthy
1030 – 1100	Morning Break
1100 – 1230	**Session 2A:** ***Keynote address: Sonographic characterization of solid breast nodules*** Thomas Stavros Chair: Nehmat Houssami **Session 2B: BreastScreening in Australia – Are we reaching our targets?** ***Quality management the key to achievement for the BreastScreen Australia Program*** Jennifer Muller ***Radiologist performance audits and training*** Mary Rickard ***Discussion*** Faculty
1230 – 1330	Lunch
1330 – 1500	**Session 3: Proffered Papers** Chair: Michael Izard ***Intraoperative examination of sentinel lymph nodes in breast cancer using imprint cytology – A review of our recent experience*** Nirmala Pathmanathan ***Positive lumpectomy margins: Is re-excision always necessary?*** Patsy Soon ***The effects of adjuvant chemotherapy for treatment of breast cancer on cognitive functioning*** Toni Jones ***Update on the RACS SNAC Trial*** Neil Wetzig for the SNAC Group ***Clinical experience of the first digital mammographic unit in Australia*** Emma Pun ***Complementary therapy usage by women with breast cancer in Australia: A national survey*** Helen Zorbas ***Combination blue dye sentinel lymph node biopsy and axillary node sampling: The Edinburgh experience*** Patsy Soon ***Early versus late participation trends in the RACS SNAC Trial in operable breast cancer*** Neil Wetzig for the SNAC Group
1500 – 1530	Afternoon Break *Sponsored by Roche Products*
1530 – 1730	**Session 4: Evaluating Equivocal and Suspicious Breast Lesions** Chair: Mary Rickard ***Sonographic assessment of extent and aggressiveness of malignant breast disease*** Thomas Stavros ***Fine needle cytology; percutaneous core biopsy: The pathologist's perspective*** Shahla Masood ***Fine needle cytology; percutaneous core biopsy: The radiologist's perspective*** Jennifer Cawson ***Breast MRI – Current indications and role in an Australian diagnostic clinic*** Kerry McMahon ***Discussion*** Faculty
1730 – 1900	Networking Drinks *Sponsored by Novartis Oncology*
1830-1930	*Breast physicians – Annual General Meeting*

Saturday 24 September 2005

0730 – 0845	*Breakfast – ASBD Annual General Meeting*
0830 – 1030	*Consumer Workshop*
0900 – 1030	**Session 5: Consensus Development Guidelines for Breast Cancer** Chair: Jennet Harvey ***The optimal pathology report*** Shahla Masood ***Quality assurance in immunohistochemistry – The Australian perspective*** Glenn Francis ***Update and development of NBCC guidelines for breast cancer*** Helen Zorbas ***The Royal Australasian College of Surgeons National Breast Cancer Audit*** James Kollias ***Guidelines for radiation therapy*** Susan Pendlebury ***Discussion*** Faculty
1030 – 1100	Morning Break
1100 – 1230	**Session 6: Survivorship in Breast Cancer / Patient Outcomes** Chair: Marie-Frances Burke ***A consumer's perspective*** Veronica Macaulay-Cross ***Locoregional morbidity of breast cancer treatment*** Hiram Cody ***The long term effects of breast cancer treatment on patient well being*** Nicole McCarthy ***Quality of life assessment in breast cancer*** Martin Stockler
1230 – 1330	Lunch
1330 – 1500	**Session 7: Breast Cancer in Society** Chair: Robin Stuart-Harris ***Epidemiology of breast cancer*** David Roder ***Counting the costs of cancer*** James Bishop ***Complementary and alternative methods of cancer treatment and drug interactions*** Treasure McGuire ***Why do people use complementary and alternative therapies?*** Geoffrey Beadle ***Discussion*** Faculty
1500 – 1530	Afternoon Break
1530 – 1700	**Session 8: Looking to the Future** Chair: Warwick Lee ***Future directions – A surgical perspective*** Hiram Cody ***The new world of systemic treatments*** Nicole McCarthy ***Biomarkers and molecular markers for evaluation of primary tumor; Ductal lavage – update on results*** Shahla Masood ***Potential future developments for breast imaging*** Thomas Stavros ***Discussion*** Faculty ***Closing comments*** Warwick Lee
1930 – 2300	Meeting Dinner *Sponsored by AstraZeneca Oncology*

SECTION 11
Abstracts

WORKSHOP

NOTES

Case presentations – Radiology / Pathology / Clinical correlation

Shahla Masood[1] and Jennifer Cawson[2]
[1]Department of Pathology, University of Florida, USA
[2] St Vincent's BreastScreen, Melbourne, Vic, Australia

NOTES

WORKSHOP

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Sentinel node / Axilla management

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WORKSHOP

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Sonographic evaluation of breast cysts that are not simple

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The percentage of all breast cysts that do not appear "simple" sonographically has increased in recent years for two reasons: 1) frequency, bandwidth, and dynamic range have been pushed to, and sometimes, beyond their limits, creating artifact within some simple cysts; and 2) improved spatial resolution has allowed us to see real echo producing material within cysts that we did not used to be able to see. Most breast cysts that do not appear to be simple lie within the huge spectrum of benign fibrocystic change and such "non-simple" cysts are too numerous to undergo biopsy or aspiration, or even to be followed. Thus, we must analyze such cysts in a manner that will allow us to comfortably classify most as benign (BIRADS 2). We must also use the "rule of multiplicity" to downgrade as many probably benign (BIRADS 3) cysts to BIRADS 2 as we possibly can.

It has taken longer to develop a logical algorithm for evaluating breast cysts than for solid nodules because the gold standard for breast cysts has until recently been less golden than the histologic gold standard that we use for solid nodules. Traditionally, the gold standard for cysts has been fluid cytology or short interval follow-up. Cyst fluid cytology has too many false positives and false negatives. Most cysts either resolve spontaneously or become less symptomatic over time, so many patients with cysts do not return for follow-up. Even surgical excision with histologic evaluation is less than ideal because the dominant cyst for which the biopsy was performed was usually ruptured in the process of histologic fixation, leading to the possibility of it being misinterpreted as background fibrocystic change rather than the main reason for the biopsy. Not until the advent of ultrasound guided directional vacuum assisted biopsy, could we precisely remove only the suspicious cyst and obtain a good histologic gold standard upon which to base an evaluation algorithm.

Within the ACR BIRADS ultrasound lexicon, breast cysts that are not simple can be characterized as "complicated" or "complex". Complicated breast cysts contain either homogeneously echogenic fluid or dependent or nondependent debris levels and can usually be characterized as BIRADS 2 or 3. Complex cysts, on the other hand, have suspicious features such as eccentric wall thickening, mural nodules, or thick isoechoic septations. Complex cysts should be characterized as BIRADS 4 or 5 and should undergo histologic evaluation with ultrasound guided DVAB with deployment of a marker in case the histology reveals malignancy or is interpreted as atypical, requiring subsequent surgical excision. Cyst aspiration with evaluation of fluid cytology is generally not adequate for complex breast cysts and may make it difficult to localize the suspicious lesion for excision should the cytology be interpreted as malignant or atypical. Any "non-simple" breast cyst that has both complicated and complex features should be classified as complex.

The algorithm that we use to evaluate "non-simple" breast cysts has been derived directly from the mammographic and sonographic solid nodule algorithms. First, we try to eliminate cysts with artifactual internal echoes, and then we look for suspicious findings. If there are no suspicious findings we look for signs of inflammation. If there are no suspicious findings we look for definitively benign findings. If we cannot identify benign findings, we try to characterize the cyst as probably benign. If we cannot characterize the cyst as benign or probably benign, we characterize it as suspicious.

First, we try to clear the cyst of artifactual echoes as best we can. On premium equipment, harmonics and spatial compounding tend to help distinguish real from artifactual echoes by building up real echoes and "averaging-out" artifactual echoes. Harmonics and spatial compounding achieve this effect by different methods, so using both is generally better for distinguishing real from artifactual internal echoes than using either alone. On mid and low end equipment, where harmonics and spatial compounding are not generally available, one should scan at lower dynamic ranges (50-55 dB) than would be used on premium equipment.

Next we look for suspicious findings.These are simply the findings that would make us characterize the cyst as complex rather than complicated – eccentric wall thickening, mural nodules, or thick septations. However, most eccentric wall thickenings and mural nodules are caused by papillary apocrine metaplasia, not papilloma or carcinoma. There are very subtle imaging findings that can help distinguish PAM from papilloma or carcinoma such as irregularity and loss of capsule at the point of attachment to the cyst wall or a duct extension from the surface of the cyst. The presence of internal vascularity is also a suspicious finding and is very helpful. PAM, no matter how florid, virtually never incites the formation of a vascular stalk. Papillomas and intracystic carcinomas, on the other hand are amongst the most vascular lesions in the breast. Thus, presence of blood flow within structures that make a cyst complex virtually excludes PAM as the cause and indicates the need for DVAB. Of course, papillomas and carcinomas frequently undergo hemorrhagic infarction, and in such

cases, would not have Doppler-demonstrable blood flow. Thus, a positive Doppler is always more useful than a negative Doppler study.

Most clustered microcysts merely contain apocrine metaplasia and lie with the spectrum of benign FCC. However, Doppler may also be helpful in such cases, because occasionally micropapillary high nuclear grade DCIS (HNG DCIS) can present as clustered microcysts. As noted above, microcysts that contain PAM will not show internal vascularity, but micropapillary DCIS often will. Thus, flow within clustered microcysts must be viewed as suspicious and warrants DVAB. Avascular clustered microcysts that are incidental and multiple should generally be characterized as BIRADS 2. However, isolated avascular clustered microcysts that present as a palpable lump or mammographic nodule should be characterized as BIRADS 3 and undergo short interval follow-up.

If there are no sonographically suspicious findings, we look for signs of inflammation or infection. If tender, such cysts might require aspiration and assessment of the fluid with gram stain and culture. Signs of inflammation include: 1) uniform isoechoic circumferential wall thickening, 2) fluid debris levels, and 3) hyperemia of the cyst wall. Most cysts showing signs of inflammation are part of the benign FCC spectrum. The fatty fluid within the benign breast cysts is prone to cause a chemical mastitis. However, even after aspiration, it cannot be determined in most cases whether the cyst is blandly inflamed or infected. The aspirate is either pus or bloody pus. Only gram stain and culture can determine this. The signs of inflammation are characteristic enough in most cases that there is no need to consider fluid cytology. Occasionally, fibrosis of the cyst wall can simulate the uniform isoechoic wall thickening seen in inflamed cysts. This is not surprising, since fibrous-walled cysts represent the healed phase in a cyst that was previously inflamed. However, cysts with thick fibrous walls generally do not contain fluid-debris levels and do not demonstrate any hyperemia within the cyst wall. The orientation of the blood vessels differs between inflamed cysts and cysts that contain papillomas or carcinomas. Vessels that supply wall of an inflamed cysts course parallel to the cyst wall. On the other hand, vessels that supply intracystic papillary lesions are merely passing through the cyst wall, and therefore, tend to course perpendicular to the cyst wall.

If there are no sonographically suspicious findings and no signs of inflammation, we can look for definitively benign findings. Most of these would enable us to characterize the cyst as complicated rather than complex – diffuse low level internal echoes, mobile echoes, fat fluid levels, and fluid debris levels. Others are merely benign mammographic findings that we have applied to ultrasound. Cysts that arise from the skin represent either sebaceous cysts or epidermal inclusion cysts. Diffuse low-level internal echoes that can be moved posteriorly by the energy of the ultrasound beam are subcellular in size and very light. Most are caused by cholesterol crystals, which are frequently present in benign breast cysts. Fat-fluid levels are far more frequently seen in ultrasound than they are mammographically. Lipid layers occur commonly in benign breast cysts. The fatty layer is echogenic and floats atop the fluid component and can be made to shift by changing the patient's position. The lipid layer is often very viscous and can require 5 minutes to shift from one part of the cyst to another. In many cases there will be multiple cysts with fat fluid levels in each breast. In such cases, it would be impractical to spend 5 minutes watching the lipid layer shift within each cyst. There are shortcuts available in such cases. First, fat-fluid levels that are in the process of shifting from one non-dependent position to another within the cyst are always obliquely oriented and sigmoid or "s"-shaped. Secondly, because the lipid layer is not attached to the cyst wall, power Doppler vocal fremitus will not cause it to vibrate and be colored. Debris levels, like lipid layers, can be made to shift. Unlike lipid layers, debris levels lie within the dependent part of the cyst. Like lipid layers, because the debris in not attached to the cyst wall, it will not transmit the power Doppler vocal fremitus artifact into the cyst. This can help distinguish tumefactive sludge from a mural nodule. Oil cysts are less definitively benign sonographically than they are mammographically. Sebaceous cysts lie so superficially, that demonstrating origin from the skin usually requires the use of an acoustic standoff. Cysts of skin origin can have three different appearances: 1) the cyst can lie entirely within the skin, 2) the cyst can lie primarily within the subcutaneous tissue, but can a "claw sign" of skin wrapping around the superficial part of the cyst can be demonstrated, or 3) the cyst can lie entirely within the skin, but the enlarged hair follicle into which the sebaceous cyst drains can be demonstrated. Since hair follicles course obliquely through the skin, "heeling-and-toeing" of the transducer may be necessary to create an angle of incidence nearly perpendicular to the hair follicle.

Finally, if definitively benign findings cannot be demonstrated, probably benign findings should be sought. Generally, these cysts have homogeneous internal echoes bright enough that they cannot be distinguished from certainty from solid nodules. There are several possible approaches to such lesions. First, they can be evaluated with Doppler. If there is internal blood flow, the nodule is either solid or an intracystic papillary lesion that completely fills the cyst. If there is no blood flow, there are several additional options. The nodule can be assumed to be solid and characterized as a solid nodule, aspiration can be attempted, or biopsy can be performed. When such lesions are assumed to be solid, there are rarely any suspicious findings and the lesion can generally be characterized as BIRADS 3. Of course, such lesions will require short interval follow-up. If aspiration is attempted, there are three possible outcomes: 1) the lesion can be aspirated completely, 2) the lesion can be aspirated partially, or 3) the lesion cannot be aspirated at all. We have found nothing that will prospectively determine which outcome will occur. The reason is that there are

four possible causes of such an appearance that all appear identical. The lesion can be completely filled with proteinaceous fluid or lipid. Such lesions can be aspirated completely with a large enough needle and enough suction. The lesion can be completely filled with apocrine metaplasia or might be solid. Such lesions cannot be aspirated at all. The lesion might be partially filled with apocrine metaplasia and partly filled with proteinaceous or fatty debris. Such lesions can be aspirated partially. When a lesion cannot be aspirated at all, manipulating the needle within the lesion can help distinguish between a PAM filled cyst and a solid nodule. PAM offers no resistance to the movement of the tip of the needle within the lesion. On the other hand, the position of the tip will be fixed within a solid nodule. Moving the tip of the needle within a PAM filled cyst can break loose enough apocrine snouts to confirm the presence of apocrine metaplasia and benign FCC.

This is certainly not the only way that cysts can be evaluated, but using this algorithm has been effective in our hands. This algorithm is long and detailed in order to show the histopathologic basis for the sonographic appearance of many "non-simple" breast cysts. However, with experience, a shorter algorithm that "works" can be used. If the non-simple cyst is round or oval in shape, completely encompassed in a thin, echogenic capsule, and has no internal blood flow, it is benign.

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WORKSHOP

A National Breast Cancer Centre Communication Skills Workshop

Effectively communicating prognosis in cancer care

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Prognosis is an issue that most health professionals and patients find difficult to discuss. Some patients may find discussing prognosis distressing and they often misunderstand the information they are given. From the health professional's perspective, issues commonly debated include how to determine what the patient wants to hear, whether to provide life expectancy estimates or make general comments, whether to discuss outliers and how to engender hope.

Effective communication between health professionals and women with breast cancer improves understanding and satisfaction with treatment and can assist women in adjusting to their diagnosis. Communication skills training workshops have been shown to be an effective tool in improving health professionals' ability to identify patient concerns, respond to their emotional cues, alleviate clinician stress and reduce burnout.

Communication skills training supports the implementation of the recommendations provided in *Clinical practice guidelines for the psychosocial care of adults with cancer*[1]. The guidelines include best practice recommendations for communicating with women with breast cancer.

The *Effectively communicating prognosis in cancer care*[2] communication skills workshop will provide an overview of the current evidence that exists in relation to discussing prognosis with women with breast cancer as well as providing practical advice and evidence-based recommendations for communicating prognosis.

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Further information about the National Breast Cancer Centre's Communication Skills Training initiative can be found at: www.nbcc.org.au/bestpractice/communication/

SESSION 1 – OPENING SESSION

Sponsored by AstraZeneca Oncology

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Keynote Address: The axilla

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The justification for axillary lymph node staging in breast cancer is threefold. Stated in order of importance, these are 1) prognostication, 2) local control of disease, and the 3) possibility of a small survival benefit. It is worth observing that patients may view the role of axillary staging differently than their physicians. Regarding prognosis, they may want to know their prognosis even if that information would not alter their treatment. Regarding local control, they may choose more radical surgery simply to avoid axillary local recurrence (LR). Regarding survival, they may choose a more radical approach even in the absence of a proven survival benefit. With recent advances in management of the axilla, patients may no longer have to choose a more radical approach to achieve all of the benefits above.

The options for axillary staging are axillary dissection (ALND), axillary sampling, sentinel lymph node (SLN) biopsy, and no axillary surgery. While many regard ALND as the "gold standard", relatively few studies directly compare ALND with other methods of staging. Two randomized trials (Edinburgh)[1,2] compare ALND with axillary sampling, one randomized trial (Milan)[3] compares ALND with SLN biopsy, and the NSABP B-04 trial compares ALND with no axillary surgery[4]. An extensive literature[5] has established SLN biopsy as a new standard operation for axillary staging, and one which offers substantial advantages over the other approaches.

Prognosis

SLN biopsy allows enhanced pathologic analysis with serial sections and/or immunohistochemical stains, methods which identify *prognostically significant* nodal metastases in 9-20%[6,7] of patients initially deemed node-negative by the standard methods used to examine ALND specimens. Viewed in this way, SLN biopsy is more important as a pathologic technique than as a surgical one. While the SLN is falsely negative in about 5% of node-positive individuals, ALND is falsely negative in 20% or more of "node-negative" cases[8] who are found to be node positive on further analysis. By allowing enhanced pathologic analysis to be done on a routine basis, the staging accuracy of SLN biopsy exceeds that of all other methods.

Local control

Axillary LR following ALND ranges from 0-2%, following axillary sampling ranges from 3-5%, and following no axillary surgery ranges from 2-20%. Of note, while 20% of patients treated without ALND in the historic NSABP B-04 trial developed axillary LR[4], more recent data show that for patients with tumors ≤1.0 cm axillary LR following no axillary treatment is only 1.7-2%. Finally, among patients with a negative SLN biopsy, we have observed axillary LR in only 0.12% of cases[9]. Reassuringly, the Milan trial[3] has found that 9% of node-positive patients in the SLN biopsy/ALND control arm had a false negative SLN, yet no patient in either arm developed axillary LR at 4 years' follow-up. Axillary LR following SLN biopsy is at least as low as that following ALND, and lower than that of the other methods.

Survival

In breast cancer, it has proven difficult to establish a relationship between local control and survival. The NSABP B-04 trial[4] found that 20% of patients treated without ALND developed axillary LR, and the B-06 trial[10] found that 40% of patients treated by breast conservation without RT developed breast LR, but that long-term survival was unaffected in either study. Both were insufficiently powered to detect small survival differences, and a recent meta-analysis pooling the results of 15 studies demonstrates that that a threefold increase (RR 3.0) in LR may increase mortality by 8%[11]. SLN biopsy can minimize axillary LR relative to other methods, but more importantly can identify occult nodal metastases missed by other methods, and better identify that subset of patients who might benefit from systemic adjuvant therapies.

Future directions

Axillary node status is at present the most important prognosticator in breast cancer, insuring a role for axillary staging for the near future. For this purpose, SLN biopsy is at least the equivalent of ALND in staging accuracy, and probably superior to it in every other aspect. SLN biopsy will have particular importance in defining a group of patients who are "truly node-negative", whose risk of systemic disease is lower than historic norms would indicate, and who do not require systemic adjuvant therapy. However, we are entering an exciting era in which tumor classification[12], prognostication[13,14], and the prediction of response to treatment[15] will be increasingly determined at the level of gene expression rather than phenotype, and era in which we can anticipate that surgical staging of the axilla will eventually become obsolete.

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Keynote Address: Borderline breast lesions

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During the last several years, increased public awareness, advances in breast imaging and enhanced screening programs have led to early breast cancer detection and attention to cancer prevention. The numbers of image-detected biopsies have increased, and pathologists are asked to provide more information with smaller tissue samples. The biopsies have resulted in detection of increasing numbers of high-risk proliferative breast disease and in situ lesions, which are considered as morphologic risk factors for breast cancer. The association between the spectrum of proliferative change and the subsequent development of breast cancer is established following publication of the studies by David Page and his colleague, and supported by other more recent results derived from the Nurses' Health Study. It is now generally agreed that the risk is estimated to be 1.5 times that of reference population for usual ductal hyperplasia and to 4-5 fold for ADH and 8-10 fold for DCIS.

The general hypothesis is that some forms of breast carcinoma may arise from established forms of ductal carcinoma in situ (DCIS), and atypical ductal hyperplasia (ADH), and possibly from more common forms of ductal hyperplasia. However, this is an over simplification of a very complex process, given the fact that majority of breast cancers appear to arise de-novo or from a yet unknown precursor lesion.

ADH has remained a controversial lesion, which shares some but not all forms of DCIS. Distinction between ADH and the grade DCIS is one of the most frequent diagnostic challenges in breast pathology. This is best reflected by several studies that have clearly demonstrated the lack of consistency in diagnosing these entities and reported the significant interobservers variability that is observed among pathologists.

Aside from morphologic similarities between ADH and the grade DCIS, biomarker studies and molecular genetic testing have shown that morphologic overlaps are reflected at the molecular level and raise questions about the validity of separating these two entities.

Controversy continues as to the optimal classification of proliferative breast disease. While majority of experts prefer to maintain the traditional terminology, there are a few who propose to use a newly proposed terminology of mammary intraepithelial neoplasia (MIN) or ductal intraepithelial neoplasia (DIN).

Columnar cell lesions of the breast represent another confusing entity, which has been recognized and described under several different names, including columnar alterations of lobules, blunt duct adenosis, cancerization of small ectatic ducts of the breast by ductal carcinoma in situ cells with apocrine snouts, columnar cell alterations with prominent apical snouts and secretions, clinging carcinoma and flat atypia. The recent renewed interest in the lesions is the result of increasing frequency of their detection because of their association with mammographic microcalcifications, morphologically, columnar cell lesions of the breast share the presence of columnar epithelial cell, lining variably dilated terminal duct lobular units with or without cytologic and architectural atypia. The degree of atypia does not necessarily imply a biologic spectrum or continuum.

The lesions are now characterized as columnar cell changes, columnar cell change with atypia, columnar cell hyperplasia and columnar cell hyperplasia with atypia. The World Health Organization Working Group on Pathology and Genetics of Tumors of the Breast has proposed the term "Flat Epithelial Atypia" for columnar cell change with atypia. Columnar cell changes with atypia do not by definition fulfill the criteria for the diagnosis of atypical ductal hyperplasia or ductal carcinoma in situ.

The clinical significance of the recognition of columnar cell of the breast is the reported association of these lesions with ductal carcinoma in situ and invasive lesions, such as tubular carcinoma and lobular lesions. More importantly, their genetic alterations are similar to those detected in adjacent ductal carcinoma in situ or invasive cancer. This association raises the possibility that columnar cell lesions of the breast may represent the earliest morphological features of malignancy. So far, however, clinical outcome studies have shown low propensity for progression to invasive carcinoma.

Currently, as with atypical ductal hyperplasia, columnar cell lesions require no further surgical management. However, those lesions associated with atypia if diagnosed by fine needle aspiration biopsy or core needle biopsy requires surgical excisional biopsy. This is because there is approximately 30% incidence of a more severe lesion in subsequent samples.

In addition, it is best to refrain from the use of the term "clinging carcinoma". Similarly columnar cell lesions of the breast should not be regarded as ductal carcinoma in situ, or even atypical ductal hyperplasia in order to avoid possibility of over treatment.

Lobular Neoplasia is another borderline breast lesion, which is referred to describe the spectrum of proliferations of epithelial cells originating in the terminal duct-lobular unit. It refers to morphologic features recognized as atypical lobular hyperplasia (AHL) and lobular carcinoma in situ (LCIS). The decision to use the term Lobular Neoplasia by Haagensen in 1978 was simply to avoid over treatment. Previous studies have clearly demonstrated that there is no prognostically significant difference between ALH and LCIS.

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Long-term studies have shown that minority of women diagnosed with LN do develop invasive carcinoma in either breast and of either ductal or lobular type. Currently, LN is considered a morphologic risk factor and a non-obligate precursor for subsequent development of breast cancer. Life long follow up with or without tamoxifen therapy is the current recorded management.

It is hoped that as one better understands the genetic basis of the spectrum of these borderline breast lesions and correlates them with the biology of the disease and patients outcome, we can better stratify these lesions. Until then, it is reasonable to assume that there are small but significant number of patients who are subject to under or over treatment.

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NOTES

Keynote Address: Neoadjuvant systemic treatment for early breast cancer

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Neoadjuvant therapy, also known as preoperative or primary therapy, is systemic therapy given before definitive locoregional treatment. Neoadjuvant chemotherapy represents standard care for locally advanced and inflammatory breast cancer. The underlying rationale for this approach relates to several important observations including: the success of this strategy for rendering inoperable locally advanced breast cancer operable, the ability to downstage large primary tumours to allow breast conservation rather than mastectomy and a compelling preclinical literature suggesting preoperative chemotherapy was associated with improved survival in a rodent breast cancer model. Hence, expectations that neoadjuvant therapy would improve clinical outcomes, increased likelihood of breast conservation and the ability to observe an in vivo assessment of treatment response have engendered enthusiasm for this approach.

The landmark NSABP B-18 study[1], randomised patients with operable breast cancer to receive either neoadjuvant doxorubicin plus cyclophosphamide (AC) or surgery followed by four cycles of AC. Long term clinical follow up has shown the disease free (DFS) and overall survival (OS) of both groups is identical. These results have been confirmed by other randomised trials and a recent meta-analysis of neoadjuvant versus adjuvant systemic treatment for breast cancer[2]. Thus, survival is not compromised by using this approach.

Much importance has been placed on the pathologic complete response (pCR) rate after neoadjuvant therapy because the women who attained a pCR in NSABP B-18 had a superior survival compared with any other group of women in the trial[1]. Most studies use pCR in the breast specimen as their primary end point, however there is emerging evidence showing that pCR achieved in the axillary nodes or breast and axillary nodes combined are more powerful predictors of survival. The predictive power of pCR has been validated in many trials and it is the best surrogate for elimination of micrometastatic disease[3].

The identification of patients with a pathologic complete response preoperatively has proven to be a difficult task. To date, the use of physical examination, mammography, ultrasound, and MRI cannot reliably predict the degree of pathologic response. Newer approaches such as functional MRI show promise and need to be validated in larger studies. Until this time, surgery must be considered a routine part of management.

Reported pCR rates using anthracycline-based therapy alone range from 6 to 19% highlighting the need for improved adjuvant therapies[4]. The incorporation of taxanes into neoadjuvant regimens has resulted in increases in pCR up to 34%[4]. The NSABP B-27 included 2 411 women with operable breast cancer and compares the combination of AC before surgery, AC followed by docetaxel before surgery and AC followed by surgery followed by docetaxel. The initial report documented a near doubling of pCR from 14% to 26% with the addition of docetaxel to the AC combination preoperatively raising the prospective of an associated improved clinical outcome[5]. However the most recent analysis at a median follow up of 5 years has shown no significant survival benefit for the addition of docetaxel either pre or post-operatively highlighting the need for more effective therapies[6]. However, pCR was still shown to correlate with superior survival. New therapies may need to have a very substantial effect on pCR before they will alter survival. The use of trastuzumab concurrent with chemotherapy has shown dramatic responses with pCR rates as high as 67%[7]. Thus the neoadjuvant setting provided early insight into the impressive survival benefits that have subsequently been demonstrated with the use of trastuzumab in the adjuvant setting.

Breast conserving surgery has become possible due to the high rates of tumour response to chemotherapy. The reported rate of conversion from mastectomy to breast conservation across neoadjuvant studies varies from 13% and 83%. But, increasing the rate of breast conservation comes at the cost of local recurrence. For example, in the NSABP B-18 trial, local recurrence rates were 16% in patients who required chemotherapy to undergo breast conservation compared with 10% for those who received lumpectomies as planned upfront[1]. This finding has been confirmed in other series. This may reflect patchy rather than concentric tumour regression after therapy which results in viable tumour foci remaining some distance away from the central residual tumour mass. Investigators at MD Anderson have identified four risk factors for local recurrence. These include advanced lymph node disease at initial presentation (N2 or N3), pathologic tumour size of >2cm, multifocal pattern of residual disease and lymphovascular space invasion[8]. The recent meta-analysis showed that neoadjuvant therapy when compared with adjuvant therapy was associated with a statistically significant increased risk of loco-regional recurrence when radiotherapy without surgery was adopted[2]. This further highlights the importance of surgery as part of routine management.

Many adjuvant studies have shown that the strongest predictor of overall survival is lymph node involvement determined at the time of surgery. Neoadjuvant therapy results in the loss of this prognostic information. Pathologic evaluation of breast and axillary nodes after neoadjuvant chemotherapy has demonstrated prognostic significance and more recently the classification of residual tumour in the breast and axillary nodes after neoadjuvant

chemotherapy using the most recent AJCC TNM system has been shown to predict distant relapse and survival. The role of sentinel node biopsy (SNB) in the neoadjuvant setting is currently being evaluated in prospective series.

Neoadjuvant endocrine therapy is an acceptable alternative to chemotherapy in the setting of a hormone receptor rich tumour that is either large but operable or locally advanced in older patients who are not candidates for chemotherapy. There have been two large Phase III neoadjuvant endocrine trials published comparing tamoxifen with one of the aromatase inhibitors confirming the feasibility of this strategy.

The preoperative setting is an excellent platform for clinical trials to investigate new agents, therapeutic targeting and treatment individualisation. It offers a platform to explore surrogate markers of response and resistance with the use of serial tumor biopsies pre-treatment, on treatment and then at the time of definitive surgery. Early identification of those who are destined to have a pCR may permit the administration of a shorter course of therapy, thereby minimizing toxicity. Conversely, the early identification of non-responders could allow prompt conversion to a second potentially more effective agent. It remains to be seen if this approach will translate into clinically meaningful gains. Clearly better drugs, improved tools to identify therapeutic response and the use of new treatment strategies will contribute to improved patient outcomes.

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SESSION 2A:

Keynote address: Sonographic characterization of solid breast nodules

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Sonographic characterization of solid breast nodules must be done with realistic goals. We cannot distinguish all benign from all solid breast nodules. It is realistic to think that we can classify 98% or more of malignant nodules as either suspicious or malignant and that we can also identify a subpopulation of solid breast nodules that are benign with 98% or greater certainty – a BI-RADS 3 subgroup. Because breast cancer is so heterogeneous, multiple suspicious findings are necessary to appropriately identify it as either suspicious or malignant in >98% of cases. No single finding can achieve this. The sonographic findings and algorithm are not unique or "wild and crazy". Six of the nine sonographic suspicious findings are simply mammographic findings applied to ultrasound and the sonographic algorithm is simply the mammographic algorithm with a couple extra steps of conservatism built into it. The main difference between mammographic findings and algorithm and the sonographic findings and algorithm is in what is easy and what is difficult. In mammography obtaining adequate images for interpretation is relatively easier and reproducible, but interpreting the images is difficult. In sonography, obtaining the appropriate images for interpretation is difficult, but interpreting technically adequate sonographic images is straight forward and relatively easier than interpreting mammograms. Obtaining adequate images requires some understanding of ultrasound physics, ultrasound machine "knobology", sonographic and Doppler techniques, an understanding of sonographic breast anatomy, and how breast cancer grows and spreads inside the breast.

The suspicious sonographic findings that we use are well based in the histopathology of breast cancer. The nine suspicious findings that we use to help detect breast cancer can be divided into typical sonographic categories of shapes, surface characteristics, and internal characteristics. However, they can also be thought of and categorized in another way. Suspicious sonographic findings for breast cancer can be thought of as hard, soft, or indeterminate – where hard findings suggest the presence of invasion, soft findings tend to represent the DCIS components of tumor, and indeterminate or mixed findings can be associated with either invasive or DCIS components of malignant breast lesions. Inclusion of "soft" suspicious findings that the presence of DCIS components is important because most invasive contain DCIS elements and these are frequently on the surface of the lesion or extend for variable distances into surrounding tissues, affecting shape and surface characteristics of the lesion. Including soft suspicious finding should improve the sensitivity for cancer and should also improve our ability to determine total extent of disease. Including soft findings should especially help appropriately characterize circumscribed invasive carcinomas and pure DCIS lesions as BIRADS 4 or 5.

Hard suspicious findings that tend to reflect invasive components of breast malignancies include: spiculation (including thick echogenic halo as and unresolved variant of spiculation), angular margins, and acoustic shadowing. Soft findings that tend to be associated with DCIS component of the lesion include microcalcifications, duct extension, and branch pattern. Mixed findings that can be associated with both invasive and DCIS components of the lesion include microlobulation, taller-than-wide orientation (not parallel in the ACR BIRDS Lexicon for ultrasound), and markedly hypoechoic internal texture. While microlobulation is, in the strictest sense, a mixed finding, it reflects the presence of DCIS components within the lesion far more frequently than it reflects invasive components.

Spiculations can be fine or coarse. Coarse spiculations present as alternating hypoechoic and hyperechoic lines radiating out from the surface of a malignant nodule. The hypoechoic component represents either fingers of invasive tumor or DCIS components of tumor growing into surrounding tissues while the hyperechoic component represents the interface between the tumor and surrounding normal breast tissues. There is a continuous spectrum between coarse spiculations and angular margins and branch pattern, so that in some cases, it may be difficult to distinguish between these findings. Fine spiculations tend to present with a single echogenicity that varies with the background echogenicity of normal breast tissue. Fine spiculations in fat surrounded lesions appear hyperechoic while fine spiculations in lesions surrounded by hyperechoic interlobular stromal fibrous tissue appear hypoechoic. Frank spiculations, both coarse and fine, are seen only in about 35% of malignant nodules on ultrasound. However, in another 36 or so per cent, there is a thick echogenic halo, that in most cases, represents unresolved spiculations. If the thick echogenic halo in considered to be a variant of spiculation, then either frank spiculations or thick echogenic halo can be found in 72% of malignant lesions.

Angular margins represent fingers of invasive tumor growing into surrounding tissues. Such angles can be acute, obtuse, or 90 degrees. A single angle on any surface of a lesion should exclude that lesion from BIRADS 3 classification. Angles occur anywhere that there is low resistance to invasion. In lesions that are surrounded by fat, angles can occur anywhere, because there is little resistance to invasion in any direction. However, in the majority of

breast cancers that arise just deep to the anterior mammary fascia, most angles occur at the bases of Cooper's ligaments. Thus, identifying Cooper's ligaments within the subcutaneous fat and following them down to where the touch the surface of a solid nodule is most useful in identifying angular margins and in appropriately characterizing invasive malignant lesions as BIRADS 4 or 5.

Acoustic shadowing is a hard finding seen in invasive malignant nodules that have abundant desmopoplasia and/or spiculation. It is most commonly seen in low grade invasive ductal carcinomas, invasive lobular carcinomas and tubular carcinomas. Because acoustic shadowing is suspicious, one should not be falsely reassured by normal or enhance though transmission in lesions that have other suspicious features. In our experience, only about one third of malignant breast lesions cause acoustic shadowing. Another third is associated with normal sound transmission and yet another third is associated with enhance retrotumoral sound transmission.

Duct extension and branch pattern are manifestations of DCIS components of tumor growing out from the main part of the tumor into surrounding ducts. Duct extension usually presents as a single projection towards the nipple, often involves the easily distensible lactiferous sinus portion of the duct, and can be up to 5 mm in diameter and several cm long. Branch pattern usually presents as multiple projections away from the nipple into the periphery of the breast. These involve smaller ducts and thus are usually much smaller and are also often shorter than duct extensions. The diameter branch patterns correlate directly with the nuclear grade of DCIS lesions, the diameter of duct extensions does not.

Microcalcifications usually occur within the necrosis in the center of the lumen of DCIS filled ducts. Microlobulations, duct extensions, and branch patterns usually represent DCIS filled ducts. Thus, it should not be surprising that classical malignant microcalcifications tend to be found in the center of microlobulations, duct extensions and branch patterns.

Microlobulations can represent fingers of invasive tumor, DCIS distended ducts, or lobules distended with DCIS (cancerized lobules). When the microlobulations are pointed and associated with a thick echogenic halo, they usually represent fingers of invasive tumor. When the microlobulations are rounded and surrounded by a thin echogenic capsule, they usually represent DCIS distended ductules and/or cancerized lobules.

Small cancers that have maximum diameters of 1 cm and less tend to be oriented into an axis that is not parallel to the skin – i.e., taller than wide. This is because such small cancers involve primarily a single TDU, and thus, reflect the shape of the TDLU in which they arose. Most TDLU's are oriented perpendicular to the skin, and thus, small cancers that arise within these TDLU's will be oriented perpendicular to the skin while the lesions are still confined to that TDLU. However, once a lesion has grown large enough to enter the main lobar duct, it rapidly grows horizontally in an axis that is roughly parallel to the skin. Thus larger lesions tend to become "wider-than-tall." However, some TDLU's at the terminal ends of lobar ducts are oriented nearly parallel to the skin, so small cancers that arise from such lobules will never be taller- than wide.

About half of breast carcinomas appear markedly hypoechoic compared to fat, the other half is nearly isoechoic or heterogeneous in echogenicity. Current equipment settings, especially high dynamic ranges, tend to "gray out" the image and may mask hypoechogenicity. Lower end equipment probably should not be operated at dynamic ranges > 50dB to maximize the chances of a malignant lesion appearing hypoechoic. Higher end equipment can frequently be operated at dynamic ranges of 65 or 70 dB or higher without "graying out" the image. Additionally, harmonics and/or spatial compounding can aid in preventing "haze" and artifact when operating at higher dynamic ranges.

None of the individual suspicious finding achieved sensitivity of 98% or greater for carcinoma, a battery of multiple findings used in a strict algorithmic approach was successful in doing so. To achieve the desired sensitivity, one must adhere to a strict algorithmic approach. A subjective approach will be less successful.

Only if there are no suspicious features do we look for specific benign findings. There are three benign findings – pure hyperechogenicity, elliptical shape, and gently lobulated shape. In any individual nodule that has no suspicious characteristics, only one of these findings needs to be present in order to characterize the lesion as BIRADS 3. All 3 do not need to be present in the same nodule.

To have an essentially 100% negative predictive value, hyperechogenicity must be as intensely hyperechoic as normal interlobular stromal fibrous tissue and must also be purely hyperechoic. Purely hyperechoic implies that there should be no isoechoic structures within the hyperechoic area that are larger than normal ducts or lobules. (< 3 mm) It is possible for a malignant nodule to have a very small hypoechoic central nidus that is surrounded by a very thick echogenic halo. If such a nodule were scanned with suboptimal sonographic technique, near field volume averaging or tangential imaging of the thick echogenic halo can falsely make such lesions appear to be purely hyperechoic.

Both elliptically shaped and gently lobulated solid nodules must be oriented parallel to the skin and encompassed completely by a thin echogenic capsule in order to qualify for a BIRADS 3 classification. Additionally, the gently lobulated lesion must have no more than 3 lobulations. Heeling and toeing the transducer and electronically steering the beam during spatial compounding can help in demonstrating the presence of a thin, echogenic capsule

on the ends of nodules where critical angle phenomena normal makes seeing the capsule difficult. Additionally, using variable compression can help demonstrate the capsule in nodules that are surrounded by hyperechoic fibrous tissue.

Combining the elliptical and gently lobulated shapes with the presence of a complete thin echogenic capsule is important in avoiding false negatives in nodules that are classified as probably benign. It particularly helps to avoid missing circumscribed invasive carcinomas and lesions composed of pure DCIS. Circumscribed malignant nodules can have a partial thin echogenic capsule in about 15 or 20% of cases, but do not have elliptical or gently lobulated shapes. Additionally, the capsule is usually incomplete. Pure DCIS has a thin echogenic capsule that represents intact ductule wall, but most DCIS lesions are microlobulated, have microcalcifications, demonstrate branch pattern, and/or duct extension.

The table below shows the efficacy of these findings and this algorithm. The sensitivity and negative predictive value are in diagnostic mode. In particular, the diagnostic sensitivity should not be confused with a screening sensitivity, which would undoubtedly be lower than diagnostic sensitivity.

Table 12-27 – Prospective characterization of solid breast nodules

	benign histology	malignant histology	
negative US (BIRADS 2,3)	245(TN)	1 (FN)	246
positive US (BIRADS 4a,4b,5)	559 (FP)	406 (TP)	965
	804	407	1211

Sensitivity = 406 / 407 = 99.8%
Negative Predictive value = 245/246 = 99.6%
Specificity = 245 / 804 = 30.5%
Positive Predictive value = 406 / 965 = 42.1%
Accuracy = (245 + 406) / 1211 = 53.8%

Patients who have nodules characterized as BIRADS 3 are offered options of:

1) 6 month follow-up ultrasound,
2) needle biopsy, or
3) surgical excision.

Whether the nodule is palpable does not alter the options offered. However, it may affect the option the patient chooses. It is more likely that a patient with a palpable lump will choose biopsy than will a patient with an incidental nonpalpable BIRADS 3 solid nodule.

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SESSION 2B: BREASTSCREENING IN AUSTRALIA – ARE WE REACHING OUR TARGETS?

NOTES

Quality management the key to achievement for the BreastScreen Australia Program

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The BreastScreen Australia Program commenced in 1991. Since then a national network of breast cancer screening services has been established across eight States and Territories. There are 32 Screening and Assessment Services, 120 associated screening units, 30 mobiles and 5 relocatables. BreastScreen Services operate in over 500 locations. In the period 1996 to 2002 BreastScreen Australia screened over 6.1 million women.

The Program is underpinned by a quality management infrastructure with national and State/Territory roles and responsibilities. All BreastScreen Australia services must comply with National Accreditation Standards. To monitor quality at the service, State and National level, all services collect the National Minimum Dataset using the National Data Dictionary. Monitoring and Evaluation Plans are being implemented with annual reporting undertaken by the Australian Institute of Health and Welfare. A key evaluation project commissioned by the Program is the mortality study.

Key indicators that measure the Program's performance and outcomes will be presented including participation rates, cancer detection rates and small cancer detection rates. The Program achieved a national average age standardised participation rate of 57.1% in 2002. There was a high level of equity achieved in participation across socio-economic groups but lower participation rates for Indigenous women and women from Non English speaking backgrounds. However there were significant variations in participation by regions and some variation between States and Territories.

In 2002, 63% of all invasive cancers detected by BreastScreen Australia were small cancers (15mm or less). Overall the Program has consistently maintained cancer detection rates and detection rates for small cancers at or above the national minimum standards.

Since the commencement of the BreastScreen Australia Program there has been a 24% reduction in the death rate from breast cancer in Australian women aged 50-69 years. The five year survival rate after diagnosis from breast cancer in Queensland increased from 71.4% during 1982-1985 to 86.9% between 1996-2000, similar patterns would be expected nationally.

This presentation will outline of the quality management infrastructure and the Program outcomes as measured against the aims and objectives of the Program and discuss the future challenges for the Program including population growth, workforce capacity and new technology.

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NOTES

Radiologist performance audits and training

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Radiologist performance audit is part of the Royal Australian and New Zealand College of Radiologists' Continuing Professional Development program and a requirement for involvement in BreastScreen Australia. Performance audit is recognized as a valuable guide to overall service quality and a useful tool to drive individual and service quality improvement.

BreastScreen Australia requires individual outcome audit, e.g. cancer detection rates, and uses this in conjunction with double reading and a minimum reading volume requirement to maximize the potential benefits of mammography screening.

BreastScreen NSW has carried out a review of the relationship between the mammogram reading volume of individual radiologists within BreastScreen NSW and individual cancer detection rates[1]. There is considerable debate in the literature as to whether the volume of reading carried out by an individual affects the quality of reading outcomes, and if so, as to the appropriate reading volume requirement. Clearly volume is not the sole factor influencing expertise and may not be even the major influencing factor. Currently the minimum number of reads per year required of radiologists in BreastScreen Australia is 2,000[2], and was derived from considerations of standards in the United States (480 mammograms per year)[3], the United Kingdom (5,000 mammograms per year)[4], and Canada (2,000 mammograms per year)[5].

The reading volumes of incident screens for the 133 BreastScreen NSW radiologists in 2000/2001 were grouped to determine if there was a threshold volume at which there was a significant difference in cancer detection outcome above as compared to below this volume. This threshold or cut-point was identified as an annual volume of 875 reads (see Table 1). The relative risk of cancer detection at this volume was 0.79 (95% CI 0.63 – 0.99). The cancer detection rates continued to improve to reach a plateau of approximately 40/10,000 at approximately 1500 reads per annum, above which no improvement was demonstrated. BreastScreen NSW data confirm the importance of a minimum reading volume requirement for expertise.

BreastScreen NSW gives individual readers data regarding their performance within the context of the performance results of their local Screening and Assessment Service and of the State of NSW. Confidence intervals indicate significant deviations from the BreastScreen Australia standards, and are used to indicate the need for the development of individual quality improvement plans.

A statewide BreastScreen NSW Radiology Training Program was carried out in 2001/2002 in an effort to improve screening outcomes[6]. The program was developed as a collaborative effort of the National Breast Cancer Center, the Royal Australian and New Zealand College of Radiologists and BreastScreen NSW. A project team developed a skills assessment test-set of films to measure individual performance pre and post training. Four statewide teleconferences were held to discuss screening findings and their management. Films were circulated for viewing prior to discussion at the teleconferences. Two one-day face-to-face workshops were held to address assessment issues. The training program was well received and evaluated by means of the pre and post training results of the test-set and BreastScreen NSW performance data.

Participation by the 124 eligible BreastScreen NSW radiologists in the teleconferences was approximately 50%, in the workshops approximately 70%, and in the pre and post skills assessment test-set was approximately 50%. Skills assessment results showed that post program there was a significant mean increase in sensitivity but a significant decrease in specificity. Similar findings were shown at a state level with a 20% pre-post increase in incident cancer detection and an 11% increase in recall rate. While it is not possible to accurately estimate the contribution of the training program to the observed changes in state-level outcome, the results of the training program evaluation demonstrate that the model used was an acceptable and successful one for providing continuing professional development.

Training, audit and quality improvement are closely intertwined and should be used to ensure high quality service provision.

Table 1: Relative risk of cancer detection for increasing numbers of mammograms read.

Annual number of mammograms	RR (95% CI)	p value
≤250 versus >250	0.44 (0.21-0.92)*	0.0284
≤375 versus >375	0.58 (0.39-0.86)**	0.0070
≤500 versus >500	0.59 (0.42-0.84)**	0.0029
≤625 versus >625	0.66 (0.48-0.90)**	0.0096
≤750 versus >750	0.71 (0.56-0.91)**	0.0073
≤875 versus >875	0.79 (0.63-0.99)*	0.0374
≤1000 versus >1000	0.83 (0.67-1.02)	0.0805
≤1125 versus >1125	0.85 (0.69-1.03)	0.1013
≤1250 versus >1250	0.91 (0.77-1.07)	0.2530
≤1375 versus >1375	1.00 (0.86-1.16)	0.9670
≤1500 versus >1500	0.99 (0.87-1.14)	0.9211

* $p<0.05$, ** $p<0.01$
RR = Relative Risk and CI = Confidence Interval.
Referent group is equal to 1.00, and is always the higher category.
Note: For increments above 1,500 mammograms, Relative Risk estimates ranged from 0.96-1.06 and did not differ significantly from 1.00.

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NOTES

SESSION 3: PROFFERED PAPERS

Intraoperative examination of sentinel lymph nodes in breast cancer using imprint cytology – A review of our recent experience

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Background and purpose

Intraoperative assessment of sentinel lymph nodes is a sound strategy as it allows for a small group of patients with positive sentinel lymph nodes to proceed directly to axillary clearance as a one stage procedure. At ICPMR we have recently (in the last 10 months) begun intraoperative cytologic assessment of sentinel lymph nodes, and we felt it would be useful at this juncture to examine our practices and results to ensure that they are comparable to those outlined in the literature and with a view to improving our diagnostic accuracy.

Methods

The literature was reviewed to compare our methods of preparation of imprints and subsequent permanent sections, to those outlined in the literature. All 60 cases of sentinel lymph nodes for breast cancer which had been assessed by intraoperative imprint cytology to date were reviewed. Cases which were subsequently proven to be false negatives on permanent paraffin sections (H&E and immunohistochemistry) were then reviewed.

Results

9 false negatives (15%) and no false positive cases were reported. On review of the cytologic preparations in these 9 cases, 7 cases confirmed the absence of diagnostic malignant cells. These 7 cases included 5 micrometastases (as defined by the AJCC guidelines) and one case of isolated tumour cells seen in the immunohistochemical stains of the permanent paraffin sections. The seventh case in this group showed a 3mm deposit which only became evident in the deeper permanent sections of the node and was not seen in the initial levels. In 2 cases malignant cells were identified in the imprint preparations, one was an invasive lobular carcinoma and the other a tubular carcinoma (grade 1) with only a single group of malignant cells seen in the imprints.

Conclusions

Although our case numbers are small, we have found our practices and results to be comparable to studies in the literature. Imprint cytology has advantages over frozen section examination as there is no wastage of material in the cryostat, is more cost and time efficient and simple to do without the assistance of technical staff.

The challenge of imprint cytology is to reduce the false negative rate (whilst keeping the false positive rate as close as possible to zero). We found micrometastases and invasive lobular carcinomas to be a significant cause of false negative results. This concurs with most studies in the literature. Increased detection of nodal metastases may be achieved by slicing the node into 2-3mm slices and examining each face, as well as possibly the use of rapid immunostaining (which also has its own problems of cost, time and artefact related interpretation difficulties). Increasing the detection rate of low grade cancers and invasive lobular carcinomas requires greater experience and diagnostic expertise, and this should not come at the cost of an increased false positive rate.

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Positive lumpectomy margins: Is re-excision always necessary?

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Background and purpose

Involved surgical margins of lumpectomy specimens are associated with increased local recurrence rates. Only 30-40% of re-excisions, however, contain further tumour. The aim of this paper was to determine if there are any histological factors which can predict a subgroup of patients with positive surgical margins who do not require re-excisions.

Methods

This is a retrospective review of 155 patients requiring re-excision for positive margins, defined as <1 mm margin for invasive cancer or ductal carcinoma in situ (DCIS).

Results

Ninety-nine patients (64%) had negative re-excisions while 56 (36%) had residual disease on re-excision. The mean age, size, grade and palpability of the cancers were similar between the 2 groups. There was a higher proportion of patients with lobular subtype and node positive disease in the positive re-excision group as compared to the negative re-excision group.

Conclusions

In this study, only 36% of patients undergoing re-excisions for positive margins had further disease. There was a statistically significant number of patients with lobular subtype in the positive re-excisions group ($p = 0.02$). While there was a higher proportion of patients with involved axillary lymph nodes in the positive re-excisions group, this was not statistically significant ($p = 0.06$). We did not, however, identify a particular factor which would predict for a subgroup of patients who would have negative re-excisions. All positive margins should therefore be re-excised.

The effects of adjuvant chemotherapy for treatment of breast cancer on cognitive functioning

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Background and purpose

For women with early stage breast cancer, adjuvant chemotherapy promotes long-term survival, and most patients now receive chemotherapy as part of their treatment. The impact of this treatment on patients' short- and long-term cognitive functioning has become a critical issue in the literature[1]. To date, studies examining the neuropsychological effects of chemotherapy have been limited by small samples sizes, the use of insensitive cognitive tests, and lack of baseline (pre-chemotherapy) data[2]. The design and methodology of the current study addresses limitations of previous research.

Methods

Approximately 220 women with diagnoses of early breast cancer who are to have chemotherapy will be assessed using a comprehensive battery of self-report measures and neuropsychological tests. Cognitive domains examined include memory, attention, processing speed, and executive functioning (e.g. planning, reasoning). Participants are assessed at four time points: immediately prior to chemotherapy, approximately 4-weeks post-chemotherapy, and at 6-months and 18-months post-chemotherapy.

Results

To date over 100 women have participated in the initial assessment; 48 of these participants have completed second assessments. Post-chemotherapy scores are compared to participants' baseline performances using repeated measures t-tests, and partial correlation tests to control for the effects of depression/anxiety and perceived quality of life on test scores. The results indicate significant differences (in the predicted direction) on measures associated with verbal learning and memory, and cognitive processing speed. When depression/anxiety and quality of life perceptions are considered, only memory for verbal learning remained significant.

Conclusions

Preliminary results of an investigation of acute cognitive changes associated with chemotherapy indicate that 220 participants will allow small but significant changes to be reliably identified. Based on current recruitment rates, the goal of 220 participants is viable and this study is currently the second largest in the world investigating cognition in breast cancer.

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Update on the RACS SNAC Trial

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For the SNAC Group

The RACS SNAC Trial is a multi-centre randomised controlled trial of Sentinel Node versus Axillary Clearance in the management of early breast cancer, conducted in Australia and New Zealand. The trial commenced in May 2001 and closed recruitment in May 2005, one year ahead of schedule with 1080 patients.

The details of the trial will be outlined in the presentation and recruitment information presented. 540 patients have been entered into each arm of the trial. 99% of patients have completed 1 month of follow-up and 12% three years of the planned 5 year follow up. In the Sentinel Node biopsy followed by immediate Axillary Clearance component of the trial, 28% of patients had a positive sentinel node and in 4% the sentinel node was not located. In the sentinel node alone component, the sentinel node was found in each case.

Fifty seven percent of patients were screen detected and 44% of tumours were impalpable. Most were treated with breast conservation but 11% underwent a mastectomy.

Lymphoscintography detected the sentinel node in 90% of cases and blue dye in 85%. 91% of sentinel nodes were in the axilla and only 6% in the internal mammary chain. The mean lymph node yield in those undergoing axillary dissection was 14.6.

The overall sensitivity for sentinel node biopsy was 92% with a specificity of 100% and an 8% false negative rate. The false negative rate was lowest (0%) with smaller tumours less than 1cm in diameter, increasing with size of the tumour.

Other information regarding length of hospital stay and drain usage will be discussed. Details of proposed further studies will be mentioned.

Clinical experience of the first digital mammographic unit in Australia

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Background and purpose

Digital mammography has been shown to be equal to screen film mammography in cancer detection and more sensitive in detection of microcalcifications. The first Australian digital mammographic unit (Selenia Lorad) was installed at Peter Mac which is a quaternary institution and Australia's only dedicated cancer centre. The purpose of our study is to evaluate the use of our digital mammographic unit in its first year.

Method and patients

1207 mammographic studies and 50 hookwire localization, were performed during the first year of use (April 2004-2005). Women aged 21-95 years (mean 59 years). 26% were first mammograms at Peter Mac while 74% were follow up studies. 24% were unilateral mammograms while 76% were bilateral. The main clinical indication was for follow up of previous breast cancer (69.6%), other indications included familial cancer screening (9.8%) and previous DCIS (4.7%).

Results

No suspicious findings were detected in 1064 (88%) mammograms. There were 56 (4.6%) cases in which indeterminate/suspicious calcifications were identified. Of these, 26 were recommended to have a repeat mammogram in 6/12. In this group, one developed a new mass on her repeat mammogram, which was an invasive ductal carcinoma on biopsy, and 17 were stable on follow up. Stereotaxic biopsy was recommended in 27 patients. In 2 cases, the calcifications seen on digital mammography could not be identified. The remainder of the biopsies demonstrated invasive carcinoma in 1 case, DCIS in 3 cases and benign disease in 8 cases. There were 16 (1.3%) cases of biopsy proven carcinoma which manifested as suspicious mass lesions or architectural distortion. Hookwire localization time was decreased using the digital mammographic machine.

Conclusion

Digital mammography has been successfully implemented at Peter Mac. Our initial experience suggests increased sensitivity at detecting microcalcifications but its clinical impact and full capabilities are yet to be evaluated.

Complementary therapy usage by women with breast cancer in Australia: A national survey

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Background and purpose

It is estimated that more than half of the Australian population use complementary therapies. Cancer patients are more likely to use complementary therapies than members of the general population, and those most likely to use complementary therapies are women with breast cancer.[1] A study conducted in NSW suggested that reasons for using complementary therapies include a preference for natural therapies and an impression that these therapies are non-toxic.[2]

There is currently limited evidence about the benefits of individual complementary therapies, with the strongest evidence supporting the use of relaxation and meditation therapies.

The National Breast Cancer Centre has undertaken a national survey of complementary therapy usage by women with breast cancer in Australia to inform the development of evidence-based information.

Methods

A self-completed questionnaire was developed following focus groups with input from a multidisciplinary project team and mailed to a national sample of 500 women diagnosed with breast cancer. Survey results will be available in August 2005.

Results

Results will identify the most common complementary therapies used by women after diagnosis, during treatment and after treatment for early and advanced breast cancer. Demographic information will also allow assessment of these results by age group and geographic location.

Conclusions

It is important that evidence-based information is developed to inform women and clinicians about the potential benefits and harms of commonly used complementary therapies. The results of this national survey will identify priority topics for evidence review.

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Combination blue dye sentinel lymph node biopsy and axillary node sampling: The Edinburgh experience

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Background and purpose

Axillary lymph node status is an important prognostic factor for breast cancer. The axilla can be staged by axillary dissection, 4-node axillary sampling or sentinel lymph node biopsy (SLNB). At the Edinburgh Breast Unit, our practice has been to perform axillary node sampling in patients with breast cancers of under 2 cm to stage the axilla. Unlike axillary node sampling, SLNB enables localization of lymph nodes. We therefore combined 4-node axillary sampling with blue dye SLNB. This allows some localization of the lymph nodes while overcoming any possibility of involved lymph nodes failing to take up blue dye.

Methods

This is a retrospective study of 107 patients who underwent a combination of blue dye SLNB and axillary lymph node sampling. A minimum of 4 lymph nodes were removed.

Results

In this audit, the mean number of lymph nodes biopsied was 5.3, with a mean of 2.7 sentinel lymph nodes and 2.7 axillary nodes. Seventeen (16%) patients had a positive sentinel lymph node and 4 patients (4%) had an involved axillary node. Of the 4 patients with a positive axillary node sample, 1 had a negative sentinel lymph node, giving a minimum false negative rate of 1% for blue dye SLNB.

Conclusions

This audit indicates that combination blue dye SLNB and 4-node axillary sampling has improved sensitivity over that of blue dye SLNB alone and may be useful as an alternative in hospitals without nuclear medicine capabilities.

Early versus late participation trends in the RACS SNAC Trial in operable breast cancer

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For the SNAC Group.

The RACS SNAC Trial commenced in May 2001. Thirty two participating centres randomized 1080 patients when the trial closed recruitment on 6th May 2005.

When the trial started, logs were kept of all patients with breast cancer presenting to 10 participating centres from November 2001 to September 2002. Similar logs were been repeated from February to March 2004 to assess if there had been a change in the views of women regarding participation and Sentinel Node Biopsy in general. Particular attention was paid to those patients who were not eligible or chose not to participate.

The number of eligible patients changed little in the two periods (46% and 44%). Surgeons offered entry to eligible patients in similar numbers (92% and 86%) however recruitment dropped from 63% to 44%.

Reasons for ineligibility changed little. Larger tumours (32% and 29%), DCIS (21% and 23%) and multi-centric cancer (14% and 9%) were the commonest reasons for ineligibility. Few women expressed concerns about entering clinical trials. In the first study 38% stated they declined participation because they wanted to choose their treatment rather than submit to randomisation but this increased to 88% in the second series. When they did choose, twice as many chose AC over SNB (65% cf. 35%) in the first series whereas more women chose SNB in the second series (48% SNB cf. 52% AC).

The randomised controlled trial has now concluded. This study shows that even though the results of this trial are not yet available, Australian women are choosing SNB based management for breast cancer in increasing numbers.

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SESSION 4: EVALUATING EQUIVOCAL AND SUSPICIOUS BREAST LESIONS

Sonographic assessment of extent and aggressiveness of malignant breast disease

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While contrast enhanced MRI is generally considered the modality of choice for staging malignant breast disease and PET/CT is considered the modality of choice for staging distant spread, ultrasound (US) can also be used to assess local extent of malignant breast disease in many patients. Most patients will undergo breast sonography prior to breast MR or PET/CT. Thus, US offers us our first chance to determine local extent of disease in many cases. US is good enough at "staging" that in any patient with solid nodule that is characterized as BIRADS 4 or 5, we routinely perform whole breast ultrasound and assess the axillary lymph nodes during the initial sonogram or immediately prior to performing US-guided biopsy of the index lesion.

US staging involves determining maximum diameter of the index lesion, assessing for multifocal and multicentric disease, and looking for presence of extensive intraductal components (EIC). Regional lymph nodes can also be assessed sonographically at the same time that the suspicious index solid nodule and ipsilateral breast are evaluated. US-detected secondary and tertiary lesions can and should be "mapped out" with ultrasound guided biopsies.

Accurate US staging: 1) lead to the appropriate type of extirpative surgery, 2) minimize the number of surgeries necessary to rid the patient of disease, 3) and can minimize the risk of local recurrence. In fact, "local recurrence" is almost always residual unresected disease that was not recognized pre-operatively or intraoperatively by the surgeon. It can also obviate staging MRI and sentinel node procedures in some cases.

We then place 9 individual suspicious findings into 3 categories – "hard", "soft", and "mixed" suspicious findings. "Hard" findings suggest the presence of invasion and include: angular margins, spiculation, and acoustic shadowing. "Soft" findings suggest the presence of DCIS components and include: duct extension, branch pattern, calcifications, and most cases of microlobulation. It is important to include soft findings in the sonographic algorithm because they improve sensitivity for pure DCIS, but also because they help us to better assess the true extent of lesions that contain both invasive and intraductal components. Most invasive ductal carcinomas contain DCIS components, which frequently lie in the periphery and contribute to the surface characteristics and shape of the lesion. "Mixed" findings are not specific and can be seen with either invasive or DCIS components of the lesion and include: taller-than-wide (anti-parallel) shape, hypoechogenicity, and a minority of microlobulations.

The most basic prognostic feature of a malignant lesion is its maximum diameter. There are two different maximum diameters – the prognostic diameter used in determining TNM stage and the surgical diameter necessary to completely remove the lesion. The prognostic diameter is the maximum diameter of the invasive component of the tumor, and is represented sonographically by the largest part of the lesion that manifests hard sonographic findings. The resection diameter includes both invasive and DCIS components of the tumor and is represented sonographically by the greatest length of combined hard and soft findings in the lesion.

Multi-focal invasive carcinoma usually represents separate foci of invasion in a single malignant lesion that are connected by DCIS components of the lesion. By scanning parallel to the long axis of the mammary ducts in the region of a suspicious breast nodule we are frequently able to show "bridges" of DCIS connecting the foci of invasion.

Extensive intraductal components (EIC) increase the likelihood of local recurrence in patients who undergo breast conserving therapy. Prominent "soft" findings suggest the presence of EIC.

Certain suspicious sonographic features correlate with the histologic grade of the lesion or with the nuclear grade of the DCIS components of invasive ductal carcinomas. The presence of enhanced through-transmission deep to a suspicious solid nodule more than doubles risks that the lesion is high-grade. Shadowing favors the lesion being low or intermediate grade. The thicker the ill-defined echogenic halo relative to the size of the hypoechoic central nidus, the more likely the lesion is to be low-grade. Circumscribed malignant nodules that are surrounded by a thin echogenic capsule are more likely to be high-grade invasive ductal carcinomas or special type tumors such as colloid or medullary. Large microlobulations and branch pattern suggests a high grade lesion, intermediate sized microlobulations and branch pattern suggest an intermediate grade lesion, and very small microlobulations suggest the presence of a low grade lesion.

Once we have completely evaluated the breast to look for multifocal and multicentric disease and EIC, we proceed to evaluate the axillary lymph nodes. We evaluate the regional lymph nodes in every case where a BIRADS 4 or 5 lesion will undergo sonographically-guided biopsy. If abnormal lymph nodes are found, we perform ultrasound-guided biopsy of the lymph node. If the biopsy is positive for metastatic disease, the sentinel lymph node procedure becomes unnecessary and the patient proceeds straight to axillary dissection. If the biopsy is negative for metastatic, the patient undergoes sentinel node procedure as originally planned. There is a distinct advantage to this pattern of sonographic evaluation. The sentinel node procedure is not perfect. False negative sentinel node procedures occur in a small percentage of patients. In such cases, the cause of failure is "tumor damming". Metastases to the sentinel node block the normal lymphatic drainage through the sentinel node, causing it to go through collaterals to a higher node that may still be histologically negative. Sentinel nodes that are so grossly filled with tumor that they alter the normal lymphatic drainage pattern are easily identified as being abnormal by sonography and can easily be targeted for ultrasound guided biopsy.

There are a host of sonographic and Doppler findings that can be used to assess lymph nodes. Imaging findings include: maximum diameter, abnormal rounding of the node, abnormally hypoechoic cortex, and most importantly eccentric cortical thickening. Variations of eccentric cortical thickening include bulges or "Mickey Mouse ears" off the surface of the lymph node, convex inward "rat-bite" deformities of the echogenic lymph node mediastinum, and displacement of the mediastinum to one side of the lymph node. Of these findings, maximum diameter is the least useful. We routinely see completely normal lymph nodes of 3 or 4 cm that, nevertheless, have a very thin cortex. We also occasionally find metastases completely filling 6 or 7 mm lymph nodes.

Since lymph flows into the lymph node from the periphery, and since metastases tend to implant in the subcapsular and/or cortical sinusoids, the hallmark sonographic finding caused by metastasis is cortical thickening. Lymph nodes that are reactive or inflamed usually cause symmetrical cortical thickening. Metastases tend to cause eccentric cortical thickening early on, but as the lymph node fills with metastases, the cortical thickening may become symmetrical. Thus, eccentric cortical thickening should be assumed to be caused by metastasis until proven otherwise, but symmetrical cortical thickening is non-specific, and can occur in reactive nodes or with metastasis. In such cases we use a "tie-breaker" finding. In most cases, by rotating the transducer into an appropriate plane, we can see more than one lymph node in a single field of view. When the cause of cortical thickening is inflammation, all the nodes in a give lymph node chain will be abnormal. One may be more abnormal than the next, but we will seldom see an abnormal node immediately adjacent to an abnormal node. However, when the cause of cortical thickening is metastasis, seeing a normal node immediately adjacent to a node that is grossly abnormal morphologically is commonplace. Thus identifying a grossly abnormal lymph node immediately adjacent a normal appearing lymph node strongly suggests the presence of breast cancer metastasis within the abnormal appearing node. Evaluation of the contralateral axillary nodes can be used as a 2nd tie-breaker when necessary (usually when multiple nodes on the ipsilateral side are abnormal). The causes of inflammation and reactive nodes are usually systemic, and thus, contralateral nodules will usually appear similar to ipsilateral nodes. When ipsilateral nodes are grossly abnormal in appearance, but contralateral nodules appear sonographically normal, it should be assumed that the cause of ipsilateral adenopathy is metastasis.

Doppler findings can also be used as additional tie-breakers when imaging findings are not definitive. The histology and biologic behavior of lymph node metastases from breast cancer is identical to that of the primary lesion in the vast majority of cases. Thus, a hypervascular breast cancer primary will usually cause a hypervascular lymph node metastasis. If the pulsed Doppler spectral waveform obtained from within the substance of the primary has a high peak systolic velocity and a high resistivity index, then so will the lymph node metastasis. Additionally, the pattern of color or power Doppler demonstrable vessels feeding the lymph node can be helpful. Reactive or inflamed nodes tend to be fed by a single hilar artery that arborizes to varying degrees within the lymph node. Metastases, however, are often fed by transcapsular feeding arteries in addition to the normal hilar vessels. Such transcapsular neovascularity is incited by metastases implanted within the subcapsular or cortical sinusoids. Thus, the presence of trans-capsular feeders strongly favors metastasis. While Doppler can be helpful, as a practical matter, we usually get enough information from cortical thickness and relationship between adjacent lymph nodes, that we rarely need to go to 2nd, 3rd, or 4th order tie-breakers.

While the older literature suggested that normal internal mammary and Rotter lymph nodes were not sonographically demonstrable, with current equipment, this is no longer true. We now identify normal internal mammary and Rotter lymph nodes in the majority of patients. The internal mammary nodes are best seen in the 2nd and 3rd interspaces, adjacent the internal mammary and vein, and are usually most numerous just superior to the costal cartilages. They measure 4-6 mm in maximum diameter. Doppler may be helpful identifying the internal mammary vessels and in distinguishing lymph nodes from tortous internal mammary veins, which occur commonly in elderly women with chronic congestive right heart failure. The presence of abnormal internal mammary lymph nodes is especially important to radiation oncologists, who no longer routinely include the internal mammary lymph node chain within the radiation fields in order to minimize pericardial and myocardial complications.

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Rotter nodes that lie between the pectorals major and minor muscles are technically level 2 nodes. Normal Rotter nodes tend to be slightly larger than internal mammary nodes and measure 7-8 mm in maximum diameter. Prominent vessel course between the pectoralis major and minor muscles and Doppler may be helpful in distinguishing Rotter nodes from these vessels.

An ultrasound contrast agent is being developed for lymphatic imaging. It can be injected into the subcutaneous tissues and is rapidly picked up within lymphatic channels and carried to the lymph nodes. The lymphatic channels can readily be identifies as echogenic streaks within the breast and the contrast column moves quickly enough that it can be followed to the nearest (sentinel) lymph node in real time. The contrast turns normal cortex echogenic or white. Contrast is prevented from filling metastasis bearing areas of the lymph node cortex, creating a hypoechoic defect within the contrast filled cortex. The contrast promises to help distinguish reactive from metastatic nodes and also should help target the abnormal portion of the cortex for tissue sampling. At some point, ultrasound contrast may replace radionuclide and methylene blue dye for sentinel node imaging, but at the present time, this contrast agent, Sonazoid, is not approved for use in humans.

In summary, contrast enhanced MRI is the procedure of choice for regional staging of breast cancer, but sonography can also be useful for mapping extent of ipsilateral breast disease both prior to MRI and after MRI in "2nd look" fashion. Sonographic demonstration and multi-biopsy mapping of multifocal or multicentric disease too extensive for lumpectomy at the time of initial ultrasound guided biopsy may obviate ipsilateral MRI. Sonographic demonstration of suspicious lymph nodes and sonographically guided biopsy such nodes can obviate a sentinel node procedure and allow the patient to go straight to axillary dissection. Appropriate staging of breast cancer with contrast enhance MRI and/or sonography can minimize the chances of positive margins and local recurrence and can also minimize the number of surgical procedures necessary to completely extirpate malignant breast disease.

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Fine needle cytology; percutaneous core biopsy: The pathologist's perspective

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Since the last century, fine needle aspiration biopsy (FNAB) procedure has gone through several ups and downs. Introduced in 1930 by Martin and Ellis in New York and unrecognized in the United States, FNAB quickly found its way to Europe. Appreciated by European physicians, FNAB was welcomed as a rapid and cost effective procedure. Since then FNAB has remained the first initial diagnostic procedure in the evaluation of breast lesions.

Several years ago, changes in the United States medical economy and a growing emphasis on cost containment stimulated a renewed interest in breast FNAB. This resulted in numerous series of reports emphasizing the merits of FNAB. Breast cytomorphology became an integral part of the training of pathology residency and cytopathology fellowships. In addition, studies in the literature revealed the superiority of FNAB over core needle biopsy in palpable breast lesions and FNAB became a widely accepted practice in the United States.

However, in the last several years, increased breast screening mammography, the development of innovative localizing devices and advancement in breast imaging has changed that practice pattern. Although initially focused to nonpalpable breast lesion, core needle biopsy has gradually become the preferred sampling technique for palpable lesions as well.

Meanwhile, we learned more about the limitations of breast FNAB. In 1996, during a National Cancer Institute sponsored workshop, the category of "Atypical/Indeterminate" was included in the diagnostic terminology of breast FNAB. The rationale behind this decision was simply acknowledging that FNAB cannot reliably diagnose entities such as atypical ductal hyperplasia, low-grade carcinomas, papillary breast lesions, fibroepithelial tumors and mucinous lesions. It was also recognized that FNAB cannot distinguish between in situ versus invasive lesions. Recommendations were made to correlate the morphologic findings seen in aspirates with the clinical presentation and the breast imaging findings.

Today, we are experiencing the same trend with core needle biopsy. As more reports appear in the literature, we are beginning to recognize similar limitations with core needle biopsy. It is now generally agreed that patients who are diagnosed as having atypical ductal hyperplasia, lobular lesions, sclerosing lesions such as radical scar and papillary lesions by core needle biopsy should undergo a follow up needle localization excisional biopsy. We are also familiar with discovering invasive lesions in lumpectomy or mastectomy specimen diagnosed as in situ lesions by core biopsy. Similar to FNAB, histologic findings in core needle biopsy should be correlated with the mammographic results with consideration of an excisional biopsy if there is any discrepancy.

In addition, there are reports in the literature about the diagnostic complexity of epithelial displacement simulating pseudoinvasion in core biopsies. In core biopsy, fragmentation and small size of the specimen may create diagnostic difficulty. Artifactual distortion of the tissue and misplaced epithelial cells occasionally make the distinction between a hyperplastic process versus a malignant lesion a serious diagnostic challenge.

Overall, regardless of limitations of these procedures, both FNAB and core needle biopsy provide excellent opportunity to avoid unnecessary open biopsies. It is clear that no single procedure is good for everyone. The goal must be to choose the right procedure for every patient who puts his/her trust in our hands.

In the selection process, consideration should be given to the cost of the procedure and the patients' comfort. FNAB is less expensive than core needle biopsy, does not require anesthesia and is associated with minimal patient discomfort. In addition, FNAB is a time-challenged procedure and in palpable breast lesions has proven to be an effective tool in triaging the patients for the next best step in their management.

For nonpalpable breast lesions, core needle biopsy is an appropriate alternative. Similar to FNAB, it is important to recognize the proper application of this procedure as well as its limitations. There are several situations where percutaneous biopsy will not result in a faster and less expensive evaluation of a nonpalpable breast lesion but rather will prolong the time required for diagnosis and increase the discomfort and expense of this exercise. These situations include lesions that are close to the skin, near the chest wall, or in the axilla. Very small lesions may be totally removed, making the localization of the area for wider surgical excision difficult if needed following the diagnosis of malignancy. There are also some types of calcifications that are difficult to sample and should be avoided.

Sampling error is also a major problem. An interested and skilled pathologist is needed for an accurate interpretation of percutaneous biopsy and appropriate correlation between morphologic and radiologic findings. Nonsurgical breast sampling usually results in a specimen that is significantly smaller than those obtained by traditional excisional breast biopsy and requires special handling. Samples from each breast lesion must be identified and separately submitted for morphologic evaluation. In order to accurately access the presence or absence of calcification and to optimize histopathologic-radiographic correlation, the pathologist must have appropriate information about the location, size, number, and types of calcification and the mammographic abnormality in a given patient.

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Pathology reports for percutaneous core biopsies should include information about the histologic grade and special types, including the presence or absence of coexistent ductal carcinoma in situ as well as blood vessel and/or lymphatic vessel invasion. In the case of ductal carcinoma in situ, it is important to incorporate the architectural type, the nuclear grade, and the presence or absence of necrosis. Samples from percutaneous core biopsy can be effectively utilized for ancillary studies to provide prognostic information.

Considering the issues outlined above, it is now evident that percutaneous biopsy requires a teamwork approach among the radiologist, the pathologist, and the surgeon. Regardless of who performs the procedure, there is definitely a need for a radiologist who identifies the abnormality with breast imaging, an informed pathologist who interprets the morphologic findings, and a surgeon who establishes the choice of procedure and appropriate follow-up of his or her patient.

The issues of the selection of the patients, the performance of the procedure, the processing of the specimen, and the histopathologic interpretation of percutaneous biopsies require special attention by several specialists interested in breast disease. This attention will indeed assure the accuracy of the procedure as well as the welfare of our patients.

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Fine needle cytology; percutaneous core biopsy: The radiologist's perspective

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Needle biopsy can enhance the management of breast lesions by providing an accurate, timely and minimally invasive diagnosis. Many benign lesions can be diagnosed without surgery. Even if surgical biopsy is subsequently undertaken for a borderline lesion, the patient can be reassured by the preliminary needle biopsy diagnosis that the likelihood of malignancy is greatly reduced. For breast cancer, needle biopsy gives a preoperative diagnosis which usually allows one stage surgery to be undertaken.

There is no definitive algorithm for management of all suspicious breast lesions. Both fine needle cytology and percutaneous core biopsy can be undertaken with ultrasound or stereotactic guidance. The choice of technique depends on the availability of expert cytology, the type of lesion, the equipment available and the preference of the treating surgeon. The triple assessment approach has been shown to be very accurate.

Good cytology is quick, inexpensive and accurate, but has a higher insufficient and false negative rate in many studies than core biopsy. If the cytologist is present, the procedure can easily be repeated. Cytology from core biopsy imprints is also useful. Cytology cannot distinguish between invasive and in situ disease (DCIS), and false positive cytology is uncommon, but both can occasionally lead to overtreatment.

Image guided core biopsy is more invasive than cytology but has a very high sensitivity (approaching 100%) for mass lesions. Core biopsy is less accurate for microcalcifications and architectural distortions, due to insufficient tissue sample volumes to make a definitive diagnosis of DCIS, lobular neoplasias, radial scar and other borderline lesions. Multiple core samples and larger diameter sampling needles diminish but do not eliminate these problems, however the latter requires expensive disposables.

Correlation of the imaging and needle biopsy findings is crucial and lack of concordance is an indication for further biopsy.

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Breast MRI – Current indications and role in an Australian diagnostic clinic

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Key strategies for improving morbidity and mortality figures for breast cancer rely on early diagnosis and accurate staging within the breast, to enable appropriate surgical management, together with the development of effective therapies. As a diagnostician, diagnosis of small breast cancers (3mm and less on MRI), and more accurate staging within the breast, can both be achieved with greater sensitivity with Magnetic Resonance Imaging (MRI) then with mammography. In a diagnostic clinic, up to 10% of breast cancers may be mammographically occult. This is most likely in dense fibroglandular tissue, young women, and with certain histological types such as lobular carcinoma.[1] Repeated studies have shown a high sensitivity for breast MRI, however specificity is often lower then that of mammography. Refinements in technique, improved use of motion registration algorithms and the development of mathematical formula and computer aided detection, is progressively increasing specificity.

In Australia MRI has been limited by government policy and restriction of Medicare accredited facilities with only just over 100 sites available in Australia. As such, non orthopedic and non-CNS indications such as breast MRI frequently struggle to obtain magnet time. For this reason, the role of MRI in Australia has been somewhat limited particularly in comparison to America and the UK, where availability is less restricted. As such, in our practice at Qld X-Ray we have performed approximately just over 130 Breast MRI cases in the last 5 years – however this still forms a relatively large series for an Australian private practice. Patients selected for MRI have consequently been those with particularly complex diagnostic work-up, for whom complete diagnosis has not been achieved with standard mammography and ultrasound. As such, a large percentage of our cases are for patients with probable occult breast malignancy in whom positive axillary nodes have been biopsied, or metastatic disease of breast origin has been confirmed, however mammography and ultrasound have been normal. More recently an increasing demand is arising from high risk women – particularly BRCA gene carriers, women with a particularly strong family history, or those with previous mammographically occult malignancy which was diagnosed by other means. A number of patients are also presenting for evaluation of prosthetic rupture or investigation of lesions overlying an implant for which mammography has not been possible.

Review of the literature outlines 5 distinct indications for Breast MRI:

1. Malignant axillary lymph node with negative mammography and ultrasound.
2. Local staging within the breast or contralateral breast prior to conservative therapy.
3. High Risk Patients – BRCA gene carriers, >2 1st degree relatives with breast cancer.
4. Differentiation of tumour from scar tissue in the post-operative/post-radiotherapy breast.
5. Assessment of implant integrity and lesions overlying an implant when mammography is not possible.

Its role in negative mammography and ultrasound in the presence of proven axillary adenopathy or metastatic disease of breast origin is unquestionable. We have performed MRI for this indication in 23 patients, (approxiamtely 20% of case load) and have found an 85% sensitivity, and an accuracy of 87%, similar to that in published data. Frequently the cancers diagnosed are small – many 3-6mm in size and hence the difficulty with mammogram and ultrasound diagnosis, and 50% of the patients have consequently been eligible for conservative therapy.

Local Staging within the ipsilateral and contralateral breast has not been an indication for assessment at our centre, however is routine in many American institutions. Studies have shown up to 30% ipsilateral additional tumours to be diagnosed and 9% contralateral breast cancers.[2,3,4] This indication is therefore likely to form an increasing patient load over the next 5 years as more clinicians become aware of the benefits of pre-operative staging and as techniques increase specificity and decrease the false positive rate.

High Risk Patients – In the initial years of our experience with Breast MRI, this group comprised a very small patients load, however in the last 12 months, this is becoming the most common cause for presentation. Included with this group, are patients with previous mammographically occult cancers. Recent publication of the MARIBS trial[5] shows MRI is more sensitive in high risk patients however its positive predictive value has been no better then mammography. Trials in the Netherlands[6] have also shown MRI to be advantageous over mammography in high risk patients. As such, motivated patients are becoming increasingly aware of this new technology and are now forming a large percentage of our patient population.

Differentiation of tumour from Scar Tissue in the Post-Operative and Post-Radiotherapy Breast: At this stage we only perform MR for this indication in difficult imaging settings – predominantly those with quite significant scarring and for whom both mammography and ultrasound offer poor sensitivity.

Assessment of Implant Integrity, and lesions overlying an implant: These referrals were very few in the first 2 years of offering the service, however have been steadily increasing over the last 2 years. They are generally from plastic surgeons and remain relatively low in numbers – with most surgeons replacing implants predominantly on a clinical basis. There have however been patients with implant rupture and free silicone within the breast for whom mammography is of low yield and for whom MRI examination has been performed to differentiate malignancy from granulomatous change or to screen the overlying breast tissue.

The high sensitivity of MRI has been quoted as varying from 80-95%. The specificity has however been variable with papers quoting between 35-80%. Continual improvement in techniques and the use of complex mathematical algorithms and post processing of large volumes of imaging data, is achieving an increase in the specificity of MRI. In collaboration with the University of Qld and the Centre of Image Analysis, Uppsala University, Sweden, we are participating in the development of software tools using pixel-mapping/parametric analysis and grid-computing to integrate more specific enhancement kinetic data, morphological and textural patterns to refine and improve lesion detection and specificity. Computer Aided Detection (CAD) in MR mammography is the subject of research at multiple institutions around the world and promises significant future advancements in achieving higher specificities to MR interpretation.

As yet we do not perform MR guided biopsies, however we do perform MR guided pre-operative wire localizations. When a lesion is identified on MRI and classified as highly suspicious of malignancy, we have been able to identify it with retrospective intense targeted ultrasound in approximately 80% of cases. For those in whom we have not been able to locate the lesion on ultrasound, we have performed MR guided localization. This involves a simple Perspex plate with 10mm regular holes in a grid, similar to that used for mammographic localizations, strapped to the breast with light compression. After localizing the skin position of shortest and most direct access to the lesion, an MR compatible wire is placed under free hand guidance and reviewed with repeat MR examination of the region, and adjusted if required.

The role of MRI is likely to dramatically increase in Australia over the next few years, particularly as software and computer algorithms improve, and research into CAD systems results in commercially available software. Most work is currently performed on 1.5T magnets, with little in the literature at this stage on 3T Magnets. As however 3T Magnets increase in availability, new techniques may become available, also contributing to changes in specificity and sensitivities. High magnet strength allows improved MR spectroscopy which offers an exciting area of research in assessing the response to chemotherapy. Clinical trials are currently in process assessing the response to chemotherapy within 24 hours after the 1st dose, enabling individualization of therapeutic regimens according to response.[7]

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NOTES

SESSION 5: CONSENSUS DEVELOPMENT GUIDELINES FOR BREAST CANCER

The optimal pathology report

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Breast cancer remains to be a major public health problem across the globe. This is a disease with no known cause or cure and respects no boundary. Like a silent enemy, breast cancer presents itself in a variety of forms and shapes and strikes in different times and different places. Breast cancer is not only a systemic disease causing major physical impairment but is also associated with significant psychosexual problems. Breasts play an important role in a woman's sexuality and self-image. For many women the loss of a breast as a result of breast cancer parallels the loss of their sexual identity.

As a serious global disease, breast cancer has received tremendous attention from researchers, clinicians, technologists, epidemiologists, geneticists, social workers, and more importantly the people at large. Increased public awareness has been one of the major milestones that has resulted in brining the people, the government and the private organizations together to fight against this devastating disease. Patient advocates have been most effective in highlighting the value of early detection and increased funding for breast research. As we move towards October, the "National Breast Cancer Awareness Month" we must salute the patients and the advocacy group for their incredible efforts.

During recent years, advances in breast imaging and genetics, introduction of minimally invasive diagnostic and therapeutic modalities, as well as molecular targeted therapy have made significant progress in enhancing the quality of life for many breast cancer patients. There has also been a remarkable change in the fundamental understanding of this disease. Breast cancer is no longer viewed as a single localized disease with radical surgery as the only alternative. Breast cancer is a heterogeneous systemic disease, which requires attention of an integrated team of knowledgeable and interested physicians and health care providers who believe in a multidisciplinary approach in breast health care as well as research and education.

The magnitude of the importance of breast cancer has inspired establishment of breast health centers focused to fostering individualized therapies. Attempts are also underway to suggest specialized training for those who are involved in the delivery of breast health care. This approach also highlights the necessity to develop effective tools for appropriate communications among the physicians, health care providers and the patients about the characteristics of a disease process. Pathologists play a significant role in this endeavor. Pathologic examination of cellular/tissue specimen provides the most critical information about the nature of an abnormality detected in breast of a patient.

Among all the disciplines involved in the study and management of patients with breast lesions, pathologists carry the most critical responsibility of providing the "last words." This is a cross road that defines the course of a disease and the future of a patient. Pathology report must include pertinent diagnostic and prognostic information. The extent of this information depends on the type of the procedures used to sample a lesion.

With increased interest in the use of minimally diagnostic procedures such as fine needle aspiration biopsy and core needle biopsy, attempts have been made to develop guidelines that can maximize the efficiency of a pathology report. Aside from rendering an accurate diagnosis, minimally invasive procedure often can offer prognostic/predictive information, which includes histologic type, nuclear grade, and the status of the expression of hormone receptor and HER-2/neu oncogene proteins. Minimally invasive procedures have recognized limitations to reliably diagnose borderline breast lesions, papillary lesions, fibroepithelial tumors, mucinous and sclerosing lesions.

Pathology reports should include recommendations for a follow up surgical biopsy. Complete excision other than total mastectomy with or without axillary contents and total mastectomy each require detailed and complete diagnostic and prognostic information. These include microscopic information such as specimen type, type of lymph node sampling, specimen size, laterality and tumor site. Microscopic information must include size of invasive component, histologic type, histologic grade, pathologic stage, the status of margin involvement and the status of lymphovascular invasion.

Tissue must also be analyzed for the presence or absence of hormone receptor protein. With the availability of Herceptin therapy, it is also critical to measure the status of overexpression or gene amplification of HER/2 neu oncogene by the established standard procedures of immunocytochemistry and Flounesence Insitu Hybridization technology. Analysis of other biomarkers remains optional.

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NOTES

Quality Assurance in immunohistochemistry – The Australian perspective

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Introduction

Treatment decisions for breast cancer patients are based on an analysis of hormone receptor status and HER2 status in the tumour. Assessment of hormone receptor status in breast cancer is by immunohistochemistry (IHC) and this is also the most common method used to evaluate HER2 status in breast carcinoma. Oestrogen receptor, progesterone receptor and HER2 are assessed semiquantitatively and accurate results are essential for appropriate patient care.

The immunohistochemistry Quality Assurance Program (QAP) breast markers module was introduced in Australia, New Zealand and South-East Asia in 2003 as an addition to the technical and diagnostic modules in IHC. Other countries have similarly introduced quality assurance programs[1, 2].

Methods

The Breast Markers module consists of two technical exercises per year with assessment of oestrogen receptor, progesterone receptor and HER2. Four slides are sent to participants comprising a tissue microarray block consisting of two cores of tissue from three tumours.

Homogeneity and stability testing are performed on the sections and every 20th section is stained to ensure representative tissue. IHC was also performed on slides over a period of 4 months to ensure antigenic site stability.

Slides are stained by the participating laboratory and returned for evaluation by a committee of scientists and a pathologist. Each slide is evaluated independently and an average score is returned. Each slide is scored from 0 to 5. The assessment criteria used are:

- Intensity of true positivity
- Good signal to noise ratio
- Distribution of staining intensity
- Localisation
- Chromogen character
- Counterstain quality
- Absence of artifacts.

A score <2.5 is considered unsatisfactory, 2.5-3.0, borderline and a score >3.0 is satisfactory. A control slide is also assessed as satisfactory, borderline or unsatisfactory.

Results

Oestrogen receptor

Sixty-six participants submitted a slide for assessment in the first survey and this increased to 76 participants in 2004. The average mark for the first survey was 2.5 and this increased to 3.2 for the second survey in 2004. Table 1 lists the percentage of satisfactory slides.

Progesterone receptor

Sixty-five participants submitted a slide for assessment in the first survey and this increased to 74 participants in 2004. The average mark for the first survey was 3.4 and 3.7 for the second survey in 2004. Table 2 lists the percentage of satisfactory slides.

HER2

Forty-three participants submitted a slide for assessment in the first survey and 52 participants in 2004. The average mark for the first survey was 4.0 and this decreased to 3.7 for the second survey in 2004. Table 3 lists the percentage of satisfactory slides.

Discussion

The initial exercise showed variation in the results for oestrogen receptor, progesterone receptor and HER2 with oestrogen receptor relatively poorly performed. The test slides are a composite of different specimens that had been submitted to the QAP for inclusion into the program, and as such would be representative of the routine laboratory material. The tumours selected attempt to span the range of results seen in clinical practice with strong, moderate and weak tumours included in various mixtures and the IHC results correlate with the tumour morphology. The majority of the sections had normal breast tissue included as an internal control. Identical tissue is included in a number of exercises to assess consistency of testing over time.

Whilst there is some variation in the results over time it is pleasing to note an improvement in the number of satisfactory slides returned for assessment.

The poor performance in oestrogen receptors is similar to that noted in other studies[3]. Initial problems with oestrogen receptor in the quality assurance program highlighted the need for selection of adequate controls. The majority of participants initially used a strongly positive tumour as a positive control, but this did not detect reductions in sensitivity at the lower end of the spectrum.

Progesterone receptor staining was well performed with the majority of participants achieving good results. The difference between the results of oestrogen receptor and progesterone receptor is striking. This may reflect the stability of the antigens or antibody affinity.

Staining for HER2 was generally well performed in comparison to oestrogen receptor.

Immunohistochemistry staining for HER2 was introduced to determine the eligibility of patients for trastuzumab. Associated with the introduction of HER2 testing into routine practice there was an educational exercise performed in 2002 and dissemination of information on laboratory techniques and interpretation of results[4]. This is in contrast to the development of immunohistochemistry for oestrogen receptor and progesterone receptor, which developed over time.

Conclusion

High quality IHC results are essential to enable treating clinicians to optimise therapy for breast cancer patients. The introduction of a specific quality assurance module for immunohistochemistry in breast cancer has enabled an ongoing assessment of the performance of oestrogen receptor, progesterone receptor and HER2 in Australia, New Zealand and South-East Asia. This had previously been performed sporadically in the immunohistochemistry technical exercise. Despite the extraction of large amounts of information in regards to the methodology used for staining, it was not possible to identify one specific method that resulted in optimal staining. Similarly, it was also not possible to identify any definitive factor in those with unsatisfactory results.

Optimisation of retrieval for a wide range of sensitivities is considered to be the important factor in achieving satisfactory results, particularly with oestrogen receptor. Laboratories have modified their techniques in response to feedback from this program. The development of the program has resulted in an improvement in the staining quality, particularly for oestrogen receptor and the module is continuing in 2005.

Comments in this report were prepared for and on behalf of the RCPA QAP.

	IHBR03-01	IHBR03-02	IHBR04-01	IHBR04-02
Unsatisfactory	37.3%	28%	49%	14%
Borderline	40.3%	31%	25%	11%
Satisfactory	22.4%	41%	26%	75%

Table 1: Results for Oestrogen receptor IHC Breast markers module 2003 & 2004

	IHBR03-01	IHBR03-02	IHBR04-01	IHBR04-02
Unsatisfactory	6.2%	10%	13%	4%
Borderline	27.7%	13%	24%	1%
Satisfactory	66.1%	76%	63%	95%

Table 2: Results for Progesterone receptor IHC Breast markers module 2003 & 2004

	IHBR03-01	IHBR03-02	IHBR04-01	IHBR04-02
Unsatisfactory	2.3%	18%	29%	9%
Borderline	21%	18%	25%	4%
Satisfactory	76.7%	64%	46%	87%

Table 3: Results for HER2 IHC Breast markers module 2003 & 2004

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NOTES

Update and development of NBCC guidelines for breast cancer

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Evidence-based practice is now the expected norm in all areas of medicine. Prior to 1995, there were no evidence-based recommendations on which clinicians could make decisions about the care they were providing to women with breast cancer.

Since its establishment in 1995, the National Breast Cancer Centre (NBCC) has developed 20 sets of clinical recommendations as well as 9 comprehensive evidence-based guidelines. Full sets of guidelines which have gone through the NHMRC approval process take about 3 years to complete. The process is slow and resource intensive and not conducive to the incorporation of new research evidence as it emerges. In addition, the costs of production and dissemination of these resources are significant.

The challenges for NBCC and other guideline developers is to provide up-to-date evidence-based information in a timely and cost-effective manner which is acceptable and useful to the target audience.

The NBCC is currently trialling a new approach to the development of evidence-based recommendations to ensure the sustainability of its role as a trusted source of credible information to assist clinicians and consumers in making treatment decisions.

The Royal Australasian College of Surgeons National Breast Cancer Audit

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In 1995, the House of Representatives Standing Committee published a report on the management of breast cancer in Australia.[1] Breast cancer was highlighted as an area where high quality surgical management was essential to provide improved surgical outcomes and survival. A recommendation was subsequently made to the Royal Australasian College of Surgeons (RACS) to develop a compulsory form of accreditation and audit process specific to surgeons performing breast cancer surgery. In 1998, despite limited funding, the National Breast Cancer Audit (NBCA) was established. Since then, over 37,000 patient episodes of early breast cancer have been entered by approximately 300 breast surgeons, first with a PC based Microsoft Access program and then, in 2004, a secure web-based version. Although a web-based application is more technically difficult, it also affords a variety of advantages such as platform independence (PC or MacIntosh), the facility for a centralised backup routine, a relative ease of software modification and greater user accessibility.

The National Breast Cancer Audit (NBCA) is an initiative of the Breast Section of the Royal Australasian College of Surgeons, in conjunction with ASERNIP-S (Australian Safety and Efficacy Register of New Interventional Procedures-Surgical) to audit surgical practice in early breast cancer. Although the National Breast Cancer Audit is not a population database and relies on voluntary participation from full member breast surgeons of the Breast Section of the RACS, it has accumulated a significant sample size since 1998 and therefore represents an invaluable source of Australian and New Zealand data that can be used to inform on current breast cancer surgical practices. Indeed, the NBCA has now become Australia's largest resource for evaluating the surgical management of early breast cancer. Such an audit could be used to improve the quality of care for patients in Australia and New Zealand.

Recent results from the NBCA have demonstrated interesting trends in relation to breast cancer surgery and subsequent adjuvant treatment. Of 25,026 cases of invasive cancer retrieved, it was noted that most clinical parameters appeared to correlate well with previously published Australian data and current practice guidelines. The results demonstrated that -

(1) The annual percentages of screen detected rates from 1999 to 2004 did not significantly differ.

(2) Breast conserving surgery (BCS) rates of 60% remained stable during this time period. Margin involvement was noted in 5% of patients whilst an additional 9% had final margins less than 1 millimetre.

(3) Radiotherapy followed breast conserving surgery in most cases (86%) whilst mastectomy cases with a larger tumour size (>5 cm) underwent radiotherapy in only 33% of cases. If at least 4 lymph nodes were positive, radiotherapy followed mastectomy in 75% of cases.

(4) The most frequently performed axillary procedure was a level 2 dissection. Only 9% of cases underwent sentinel node biopsy (SNB) alone although there was an increase in frequency of SNB in recent years. In 9% of all invasive cases, no axillary procedure was undertaken or recorded.

(5) Chemotherapy treatment was received by 78% of oestrogen receptor negative, axillary node positive, postmenopausal patients. Tamoxifen was used in the majority (83%) of oestrogen receptor positive cases. Tamoxifen was also used in 16% of oestrogen receptor negative cases.

The initial emphasis of the NBCA was on improving practice by allowing surgeons to review their own data against the national aggregate for a number of clinical indicators. Recent emphasis has shifted towards the development of a full clinical audit cycle whereby audit data is reviewed against benchmarks in accordance with the evidence-based "Clinical Practice Guidelines – Management of Early Breast Cancer"[2]. The NBCA is overseen by a number of individuals who have professional, strategic and organisational interests in breast cancer. Key performance indicators (KPI) based on evidence-based National Guidelines have been identified and quality thresholds for surgical and clinical outcomes have been developed for each KPI (see table).

	Key Performance Indicator	Quality threshold
1	The percentage of invasive cancer patients with clear margins after breast conserving surgery	≥95%
2	Percentage of patients with invasive cancer referred for radiotherapy after breast conserving surgery	≥85%
3	The percentage of patients referred or prescribed hormonal treatment for oestrogen positive tumours	≥85%
4	The percentage of patients undergoing axillary surgery for invasive cancer	≥90%
5	The percentage of DCIS patients undergoing no axillary surgery	≥90%

NOTES

Preliminary results suggest that most cases of early breast cancer receive appropriate surgery and are referred for or receive suitable adjuvant therapy. However, some results suggest that improvements in surgery can still be achieved (ie achieving free surgical margins for cases of breast conserving surgery and avoiding axillary dissection in cases of DCIS). An outlier process has been developed which will be used to evaluate whether surgeons adhere to the benchmarks. This process was endorsed by the Council of the Royal Australasian College of Surgeons in February 2005 and ratified by Breast Section members attending the RACS Annual Scientific Congress in Perth (May 2005). The audit requires the good will of participating surgeons and the outlier process offers the possibility of providing an educative process rather than a punitive one.

Analysis of results and subsequent reportage is an essential aspect of the audit process and reports are being provided to surgeons, hospitals, State Departments of Health and the Australian Government Department of Health and Ageing. Audit data will also be analysed to strategically answer clinically relevant questions.

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Guidelines for radiation therapy

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The development of guidelines for the management of Early Breast Cancer has been in progress for over a decade. Guidelines, both National and Local have now undergone not only publication, but also an update process, ensuring they continue to reflect current published literature. In radiation oncology the guidelines encompass breast conservation, postmastectomy and DCIS. They can also be implemented for the metastatic setting.

In early invasive breast cancer, there is equivalence between mastectomy and breast conservation for tumours up to 5cm. Patients are encouraged to have their choice of surgical procedure, recognizing that factors such as breast size, co-morbidities,and the extent of pathology such as DCIS may limit the choice in some women. Fifteen randomised trials have investigated the role of radiotherapy or not after breast conserving surgery and all have shown a local control advantage for the delivery of radiotherapy. A recent meta-analysis of these trials has now demonstrated a small survival advantage. The relative risk reduction being 8.6%. The local control advantage is small in women over 70 yrs with small ER Positive, node negative tumours (3% at 5 years) and larger in younger women. While delivering the radiation dose over 25 fractions is effective, usually to 50 Gy, a randomized trial of 1234 patients has shown equivalence with a shorter fractionation schedule of 42.6 Gy in 16# for some women not receiving chemotherapy. The importance of delivering the boost dose of radiotherapy has been demonstrated in randomized trials, but is less important in older women.

Younger women, particularly those under 35 years form a special group. They are under represented in the randomized trials and there must remain some uncertainty as to whether of not breast conservation is truly equivalent to mastectomy for this group. Even after radiotherapy they remain at increased risk of local recurrence, and one large study from the EORTC linked poorer survival with those receiving breast conservation[1].

In the post mastectomy setting, radiotherapy reduces the rates of local relapse by approximately two thirds, although improvements in survival remain the subject of clinical trials. An overview[2], as well as two well known trials, the Danish and British Columbia trials have shown improvements in overall survival as great as that seen with adjuvant chemotherapy however it is difficult to generalize these results because of differences in radiotherapy techniques, treatment volumes, surgical techniques and systemic therapies. In delivering postmastectomy radiotherapy, the greastest risk of local relapse is to the chest wall, so this is treated in all volumes. The treatment of the supraclavicular field is added for patents with 4 nodes positive after a level 1 and 2 dissection, or fewer nodes if there are other risk factors. An axillary field is not routine and is added only if there is doubt about the completeness of surgery. The addition of the internal mammary node field is not routine and is the subject of clinical trials.

In DCIS, two overviews have confirmed the lowest rates of local recurrence are with mastectomy (1.8%). The randomized trials have shown a local control advantage for radiotherapy in the setting of breast conservation for all patients, when compared with lumpectomy alone.

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SESSION 6: SURVIVORSHIP IN BREAST CANCER / PATIENT OUTCOMES

A consumer's perspective

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The report of the Breast Cancer Network Australia's (BCNA) Second National Breast Cancer Conference for Women 2004 details 61 recommendations, which came from issues identified by the 600 breast cancer survivors in attendance. Some of these issues are related to survivorship. When the treatment for breast cancer is completed there can still be many issues which need attention. These can be grouped under the headings of physical changes, emotional impact, fertility and sexuality, personal relationships, fear of recurrence, genetics, long-term effects of adjuvant therapies, financial and career implications. Women need good follow up and appropriate referral. One way of achieving this is for consumers and health professionals to work together to make sure all the relevant National Breast Cancer Centre Clinical Practice Guidelines are resourced and implemented across Australia.

Locoregional morbidity of breast cancer treatment

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Axillary lymph node staging remains an essential part of breast cancer treatment, but the morbidity of axillary lymph node dissection (ALND) is well-recognized. Potential side effects include sensory changes, restriction of shoulder motion, lymphedema, and infection. After completion of treatment, patient complaints referable to the arm are more common than any others[1]. The promise of sentinel lymph node (SLN) biopsy is that all of these side effects would be minimized.

Caveats

The literature addressing the morbidity of axillary staging is problematic. Study design varies widely, and includes retrospective, prospective, case-control, and prospective randomized designs. Quality of life (QOL) assessment is infrequent and sophisticated instruments are lacking. Methods of assessment, type/duration of treatment, and follow-up differ. All studies are subject to ascertainment bias, observer bias, and patient bias. Finally, there are no large population based-studies which address incidence, severity, duration, or response to treatment for the sequelae of lymph node staging[2].

Incidence and risk factors

Ten studies (1991-2000), subject to all of the variations noted above, document an incidence of post-ALND lymphedema ranging from 0-56%[2]. An earlier classic study by Kissin et.al.[3] found that post-ALND RT substantially increased the risk of lymphedema (38%) compared to patients treated with ALND (8%), axillary sampling (9%), and axillary RT (7%). This finding has been confirmed repeatedly by other studies. Additional risks for lymphedema are infection, and heavy/obese body habitus[4]. Of note, the incidence of post-ALND cellulitis is probably far lower than that of lymphedema.

ALND vs SLN biopsy

Two non-randomized[5,6] studies and one randomized trial[7] document that the morbidity of SLN biopsy is less than that of ALND, but also show that the morbidity of SLN biopsy is not zero. An early report from the American College of Surgeons Oncology Group Z0010 Trial documents sensory morbidity in 8.6% and lymphedema in 6.9% of >5000 patients following SLN biopsy[8]. A detailed analysis comparing the sensory morbidity of ALND vs SLN biopsy reaches a similar conclusion, finding that the sensory morbidity of SLN biopsy is about half that of ALND and that both decrease over time[9]. A long-observed but newly described phenomenon, "axillary web syndrome", has been associated primarily with ALND but also reported after SLN biopsy[10]; this phenomenon is consistent with the rediscovery of Sappey's concept[11] that the lymphatics of both the breast and the arm drain to the same few lymph nodes in many patients.

Prevention and treatment

It is widely assumed that lymphedema can be avoided if patients follow a careful program of post-ALND prevention, and standard practice is to offer all such patients a detailed list of recommendations; this practice in now being carried over to patients who have had SLN biopsy alone. There is no evidence whatever that any of these measures are effective[2]. Insistence on a rigorous program of "prevention" may have the adverse effect of making patients with lymphedema feel that it is their own fault, rather than a well-recognized side effect of their breast cancer treatment.

Traditional therapy for lymphedema has included elevation, exercise, massage, compression, complex physiotherapy (PT), drugs and (rarely) surgery, with most recent reports focusing on combinations of compression and complex PT and reporting modest effects. Among 15 trials reported since 1989[2], statistically significant effects of therapy were identified in none of 3 randomized studies, and in 6 of 12 cohort studies.

Until recently, surgery for lymphedema has proven to be either ineffective or excessively morbid. Brorsen and Svensson have developed an innovative approach which combines liposuction with sleeve compression, and has achieved substantially better results than compression alone[12]. As for all methods of lymphedema treatment, lifelong sleeve compression is required to maintain the gains of therapy.

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The long term effects of breast cancer treatment on patient well being

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Earlier detection of invasive and non-invasive breast cancer and more effective treatments have led to both an improved prognosis for women with breast cancer and an increasing number of long-term survivors. Currently, the 5-year and extended disease-free survival for early stage breast cancer in Australia is approximately 85%[1]. However, such advances present various physical and emotional health challenges to patients facing breast cancer and its aftermath. Thus, an understanding of the specific medical and psychosocial problems associated with survivorship is mandatory.

The goals of follow-up are to detect breast cancer recurrence, screen for new primary breast cancer, monitor and manage long-term complications of treatment, ensure compliance with current therapy and surveillance guidelines, and address fertility and psychosocial issues. The follow-up checklist relating to long term effects includes:

1. Local complications of therapy

Surgery may be associated with long-term residual numbness, pain, lymphoedema, and limited arm movement. Local complication rates are likely to decrease as sentinel node procedures become more widely used. Long-term side effects of radiation therapy, although rare, include an increased risk of second malignancies (eg, chest wall sarcoma, ipsilateral lung cancer), rib fractures, brachial plexopathy, pneumonitis, and myocardial infarction.

2. Complications of chemotherapy

Adjuvant chemotherapy is associated with a range of complications. The risk of premature ovarian failure is related to the age of the patient as well as the chemotherapy regimen and duration of treatment. Clinically significant congestive heart failure occurs in 0.5% to 1% of women treated with standard-dose, anthracycline-based chemotherapy regimens and may occur months or years after completion of therapy[2]. Trastuzumab (Herceptin) is also associated with an increased risk of cardiac toxicity that is not dose-related and usually reverses upon cessation of therapy[3]. Myelodysplastic syndrome and acute myeloid leukemia are rare and should be considered if cytopenias develop after therapy. The cumulative incidence of leukemia is less than 1% in the majority of trials of standard anthracycline-based chemotherapy regimens[2]. The addition of taxanes has not resulted in an increased risk to date. Many women who receive adjuvant chemotherapy gain weight, with the average gain ranging from 2 to 6 kg. Postulated causes of weight gain include decreased physical activity, ovarian failure, increased food consumption, and reduced basal metabolic rate[4].

3. Complications of hormonal therapy

The most common side effects of tamoxifen include hot flashes, vaginal dryness, vaginal discharge, irregular menses, and nausea. Endometrial cancer occurs in 0.5% to 1% of women who take tamoxifen for 5 years, and the higher percentage of risk is seen in women aged 50 years and older[5]. Tamoxifen use is also associated with an increased incidence of deep venous thrombosis, pulmonary emboli, and stroke. Although these conditions occur in less than 1% of patients treated with tamoxifen, incidence increases with patient age. Aromatase inhibitors are being used increasingly as adjuvant therapy and are associated with an increased risk of fractures and musculoskeletal symptoms.

4. Menopausal symptoms

Vasomotor symptoms associated with menopause or cancer therapies present a serious problem for many breast cancer survivors, particularly those with hormone receptor positive tumours. Non-hormonal treatments with proven efficacy in reducing hot flashes include selective serotonin reuptake inhibitors, clonidine and, more recently, gabapentin. Mixed benefits have been seen with use of black cohosh and soy products and Vitamin E. Vaginal dryness and dyspareunia can be managed with non-hormonal agents such as vaginal lubricants and moisturizers. The safety of topical oestrogen in hormone receptor positive breast cancer is unknown.

5. Bone health

Most women with newly diagnosed breast cancer are at risk of osteoporosis because of their age or treatment regimen. Bone mineral densitometry should be evaluated and treatment for osteopenia/osteoporosis as per standard osteoporosis guidelines. Lifestyle recommendations include: smoking cessation, increased exercise, and daily intake of calcium (1,200 mg) and cholecalciferol (vitamin D3) (400 to 800 IU)[6].

6. Psychosocial and cognitive function

History taking should include questions about patient mood, body image, levels of fatigue and anxiety, and possible impaired cognitive performance and sexual functioning, since dissatisfaction in these areas is prevalent among survivors[7]. Psychological distress and adjustment problems are most intense during the first year after diagnosis and therapy and tend to improve over time.

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7. Pregnancy

Pregnancy after breast cancer has not been shown to be disadvantageous to survival rates. However, studies in this area are retrospective and associated with selection biases, and hence the true impact of pregnancy on relapse risk is not known. Information on the risk of assisted conception, including in vitro fertilization before or after breast cancer treatment, is even more limited.

Conclusion

Breast cancer survivors face unique health concerns related to their disease history, the ongoing risk of recurrence, and the impact of treatment on their bodies and general well-being. Follow-up visits should be focused, informative, and supportive to help facilitate a high quality of life for these patients.

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Quality of life assessment in breast cancer

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The goals of treatment for breast cancer are to improve length and quality of life. The challenges for clinical research – establishing if new treatments do either – differ according to stage. The problem in advanced disease is establishing if improvements in cancer-related symptoms outweigh impairments due to treatment-related side effects. The problem in early breast cancer is establishing if improvements in survival warrant the side effects and inconvenience. In this talk I will summarise important lessons for practice and research from recent and ongoing studies about the effects surgery, radiation, endocrine therapy and chemotherapy on quality of life and about women's preferences for these treatments.

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SESSION 7: BREAST CANCER IN SOCIETY

Epidemiology of breast cancer

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Breast cancer has been the most commonly notified cancer in Australian females since cancer registration began in this country in the early 1970s. In 2001, approximately 11,790 invasive female-breast cancers were notified to Australian cancer registries, many more than the 5,880 large-bowel cancers, which constituted the second leading category of cancer in women.[1] Around 2,590 deaths were attributed to female-breast cancer in 2001, such that this cancer remained the leading cause of cancer death in the female population.[1]

The age-standardised incidence of invasive breast cancer in Australia in 2000 was more than twice the estimated world average and about six times the lowest incidence, which was reported for Middle Africa.[2] Only North America had a higher incidence than Australia. Yet case fatality rates for female-breast cancer, as inferred from ratios of deaths to cases, were lowest for Australia and North America, such that age-standardised breast-cancer mortality rates for these populations were lower than for New Zealand, Northern Europe and Western Europe.[2]

National incidence data have been available in Australia since 1983. Between 1983 and 1989, a mean annual increase in age-standardised incidence of two to three per cent took place for invasive female-breast cancer,[3] which likely would have been inflated by the promotion of early detection during that period. The incidence increase was larger than the approximate 1% increase recorded in North America from the 1930s to 1970s,[4] when reductions in fertility and delays in childrearing are thought to have contributed.

Between 1990 and 1995, the annual increase in age-standardised incidence in Australia became larger, approximating 4%.[3] This is considered to have been artificial, reflecting increased detection from the introduction and extension of population-based mammography screening and associated early detection initiatives. Then, during 1996-2001, the scale of incidence increase reduced to about one to two per cent per annum.[3]

While age-adjusted female-breast cancer mortality rates also increased in the 1980s, by just over 1% per cent per annum, a mean annual decline of around 1% took place in 1990-95. This decline then strengthened to almost 4% per annum in 1996-2000, followed by relatively stable mortality rates in 2000-03.

The reduction in breast-cancer mortality in Australia during the 1990s has mostly been attributed to earlier diagnosis and advances in adjuvant therapy, although other treatment advances may have contributed.[5] This reduction is a particularly reassuring development, given the earlier upward trends in mortality and the continuing increases in incidence.

Data from South Australia are similar to those from other registries in pointing to a higher invasive breast cancer incidence in Australian-born than overseas-born women.[5] In particular, low age-standardised rates apply to women born in Southern Europe, Eastern Europe and Germany. While a lower incidence is also apparent among Asian-born than Australian-born women, statistical significance has not been achieved with the comparatively small numbers of these women available for analysis.[5]

Meanwhile, Indigenous women have had an age-standardised incidence about half the population average, which accords with observations in the Northern Territory.[5, 6] Separate data indicate that case fatality rates are higher in Indigenous than other women, with this outcome explained only in part by more advanced stages of disease at diagnosis.[5, 6]

Other trends in South Australia include an upper socio-economic gradient, with women residing in upper quartile postcodes (SEIFA index) having an age-standardised incidence of invasive disease about 15% higher than women in lower quartile postcodes. Small urban excesses also have applied, with metropolitan residents presenting an age-standardised incidence about 5% higher than residents of country regions.[5]

Five-year survivals from invasive female-breast cancer approximate 84% in South Australia, which is similar to the more general Australian experience.[7] Secular increases in survival have occurred in all age groups, but more so in women over 50 years of age at diagnosis. Lower survivals apply to women aged 80 years or more at diagnosis than to younger age groups. [7]

The proportion of invasive breast cancers found when small (<15mm) tripled in South Australia between the 1980-86 and 1997-2002, with 50-69 year olds (the principal mammography target) having the highest proportion of small lesions in 1997-2002.[8] Although increases in small-tumour proportions applied broadly across the population, these gains were less pronounced in women born in non-English speaking countries.[8]

While small tumour size is associated with higher survivals, decreases in size explain only about 46% of the reduction in five-year case fatality between the 1980-86 and 1997-2002 diagnostic periods. The remaining reduction likely would reflect treatment advances, plus confounding effects from lead-time, length-time and related biases.

South Australian data reveal increases in proportions of female-breast tumours classified as "in situ", from around 7% in 1989-90 to 11% in 2001-2002.[9] During 1989-2002, the "in situ" proportion was highest at 11% for 50-69 year olds, compared with 9% for younger women, 7% for 70-79 year olds, and 3% for women aged 80 years or more.[9] The natural history of "in situ" lesions is unclear and uncertainties remain as to the most appropriate clinical management.

Meanwhile, the proportion of invasive lesions classified as ductal lesions has shown a small downward trend in South Australia, from 86% in 1977-90 to less than 84% in 1997-2002.[9] By comparison, increases have occurred in the proportion of lobular lesions, from 6% in 1977-84 to 10% in 1997-2002, and of tubular lesions, from less than 1% in 1977-84 to over 3% in 1997-2002. Comparisons by age point to higher proportions of lobular and tubular lesions among 50-69 year olds than other age groups, and a higher proportion of mucinous lesions in older women, particularly among those aged 80 years or more. [9]

Hospital registry data from South Australian teaching hospitals accord with population-based data in showing reductions in tumour size.[7, 8] They also show secular improvements in other prognostic indicators such as stage, grade, nodal status and hormone receptor expression. It is notable that multivariable analyses reveal survival gains after adjusting for secular changes in these indicators, which likely would reflect treatment advances as well as confounding influences.[7]

Hospital data show an increased use of conservative surgery in preference to mastectomy for early stage disease.[7] This has been seen in all age groups. Meanwhile, adjuvant radiotherapy has become a more common part of the primary course of treatment, especially in patients receiving conservative surgery.[7] In addition, secular increases in the use of chemotherapy and hormone therapy have taken place.[7]

Hospital data also show that older patients aged 80 years or more are less likely than younger patients to receive comprehensive treatment.[7] In particular, they are less likely to receive surgery, radiotherapy and chemotherapy, after adjusting for stage and other prognostic indicators. This trend would largely reflect an increased prevalence of treatment contraindications among older women, due to increased co-morbidity and frailty. By comparison, hormone therapy is more prevalent in the older than younger age groups. [7]

Age-standardised incidence rates for invasive female-breast cancer have risen markedly in Australia since the early 1980s, by 39% between 1983-85 and 1999-2001.[3] Future trends will be subject to changes in risk factors, as may follow from further changes in reproductive behaviour, postmenopausal hormone use, age at menopause, and levels of obesity. An introduction of more sensitive diagnostic or screening technologies also would be expected to affect case numbers.

If the mean annual increase in age-standardised incidence observed since 1997 were to continue, a 14% increase would take place between 2001 and 2011. Absolute increases in case numbers would be larger again, due to increases in size and ageing of the population.

By comparison, the age-standardised mortality rate for female-breast cancer has decreased substantially in Australia, by about 20% between 1989-91 and 2001-03. If the mean annual decrease between 1990 and 2003 were to continue, a further reduction of around 13% in mortality rate would be expected between 2003 and 2011. Alternatively, this reduction would be smaller at about 6%, if trends presenting in the more stable age-standardised mortality rates in 1999-2003 were to continue.

Either way, there would not be a commensurate reduction in need for end-of-life services, in that these reductions in age-standardised mortality would be countered by effects of increasing size and ageing of the population.

It is evident that epidemiological trends for female-breast have been variable in Australia and affected by changes in risk factors, screening coverage and treatment advances. This variability has made future projections a more uncertain exercise. In these circumstances, ongoing monitoring and revision of projections will be particularly important if the best possible estimates of future service requirements are to be obtained.

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Counting the costs of cancer

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Cancer represents one of the largest health problems in Australia in terms of human and financial costs. There are over 32,000 new cases in NSW alone with 12,600 deaths each year. Cancer is responsible for 19% of the burden of disease (quality life years) in our society. In NSW alone, over $1 billion is spent annually on cancer control, with a bias for funding acute services. The major preventable cause of cancer is tobacco consumption. In NSW, this single cause accounts for over 6,000 deaths annually, including non-cancer deaths, at a cost to society of just under $7 billion per year. However, investment in screening has been shown to be cost-effective. The current breast screening programs have contributed to over 20% reduction in breast cancer mortality rates over the last 10 years at a cost of $30 million annually. Breast screening costs are a useful benchmark for identifying the costs of bowel and other screening programs in the future.

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Complementary and alternative methods of cancer treatment and drug interactions

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Background

All individuals engage in some behaviours intended to protect their health; medically sanctioned or not, objectively effective or not[1]. Cancer, in particular, is characterised by uncertainty and anxiety for patients and their family[2]. Many authors have argued that help seeking behaviours, such as self-medication, information seeking or avoidance, are coping responses to uncertainty of disease outcome, in the setting of impending health threat[3].

At any given time, one-third of the general population engages in self-medication[4], many willing to accept lower or unpredictable efficacy rather than risking prescribed medication-induced adverse effects[5]. The extent of self-medication with complementary medicines (CAMs) was demonstrated in a survey of 3,004 South Australian households, where 52.1% of individuals had used one form of CAM in the previous year[6]. Reported reasons include: ease of access; belief that natural remedies are more congruent with values and philosophical orientations toward health[7]; dissatisfaction with mainstream medicine[8] and the desire for autonomy over health decisions[1]. Self-medication can however lead to misdiagnosis, mistreatment of symptoms, or a delay in treatment of significant pathology.

In 2003, there were over 2,500 brand names and 25,000 medical devices listed on the Pharmaceutical Benefits Scheme (PBS) and the Australian market, respectively. In 2000, Australians also spent more on CAMs ($2.3 billion) than on the PBS 00 ($688 million)[6]. The sheer volume of chemical entities marketed, their potency and associated risks reflect the changing nature of medicines. Inadequate communication between consumers and their primary health carers about their CAM use means that many patients may be unaware of potential interactions between their prescribed and their self-medication.

Method

This paper describes a survey of CAM use in 100 adult Daycare Oncology patients at Mater Health Services, 51% diagnosed with breast or gynaecological cancer, to highlight prevalence of use and potential problems associated with CAMs. It also summarises adverse drug reactions and drug interactions with CAMs commonly used by cancer patients, drawn from the literature and from calls received nationally from consumers on the Adverse Medicines Events Line.

Results

1) CAM prevalence survey: Of 100 adult cancer patients, 52% had used CAMs since diagnosis and 46% were current users. Patients 35-54 years used CAMs more frequently than those >/= 55 years. A total of 175 products were taken by 52 patients, with a range of 1-9 products per person. Most commonly used were herbals (42.7%) and vitamins/minerals (37.9%). While CAMs were predominantly used for symptom relief, 11.3% were taken with the belief they "assisted" in cancer cure. These included Western, Chinese and Ayurvedic herbal medicines (e.g. gingko, ginseng, kava, mistletoe, St John's wort, valerian, laetrile, sorrel) and minerals such as selenium, shark cartilage and zinc. Significantly, 56% of CAM users had not informed their doctor of their use.

2) Potential problems associated with CAMs

CAM – adverse effects	Mechanisms
Problems inherent in the nature of herbal medicine	• Lack of product standardisation varying amount of active constituent(s) and varying positive and and/or adverse effects eg Pan Pharmaceuticals recall of Travacalm (hyoscine); • Direct toxic effects due to expected/ unexpected pharmacological action; • Use of CAMs delaying or replacing more effective conventional therapies.
Deliberate substitution/ addition of toxins or pharmaceuticals to CAMs	• eg Chinese herbs contaminated with steroids; Mexican wild yam adulterated with progesterone.
Accidental substitution or contamination	• Contamination ranging from pesticides, heavy metals to pathogenic organisms eg Chinese herbal medicines.
Improper use	• The lack of childproof containers for many CAMs • CAMs taken by non-traditional means eg recent TGA recall of kava *Piper methysticum* – case reports of hepatotoxicity.
Unrecognised or unpredicted effects	• Adverse effects due to patient age, genetics or co-morbidities; • Drug interactions with conventional and CAM combined eg serotonin syndrome due to St John's wort – antidepressant interactions; • Allergic reactions and cross-sensitivities.

3) CAM-induced adverse reactions and interactions

CAM	Constituents – Actions	Adverse Reactions	Interactions
Black Cohosh *Cimifuga racemosa eg* Remifemin	• formononetine (isoflavone) suppresses LH • acteina – hypotensive • cimigoside • steroidal terpenes	Bradycardia, hypotension, nausea, vomiting, increased perspiration, uterine stimulation	• Anaesthetics/ antihypertensives/ sedatives – increased effects • Report of tamoxifen plus black cohosh causing endometrial hyperplasia & vaginal bleeding
Blue Cohosh *Caulophyllum thictroides* root	• alkaloids eg anagyrine, methylcytosine (nicotine-like) • aaponins eg hederagenin • phytosterol, resin, starch Smooth muscle stimulant, oestrogenic, vasoconstrictor, hyperglycaemic	Chest pain, hypertension, diarrhoea, hyperglycaemia	• Antihypertensives – hypertension • Antidiabetics – may decrease efficacy) • NRT – may increase effects of nicotine
Chasteberry *Vitex agnes castus*	• volatile oils • flavonoids • iridoid glycosides • progesterone, testosterone androstenedione anti-androgenic, progestogenic. dopaminergic, anti-inflammatory	Headache, abdominal pain, diarrhoea, pruritus, rash, increased menstrual flow; Herb ceased in 1% of cases due to side-effects in Germany	• Dopamine antagonists eg antipsychotics, metoclopramide – may block action • Dopamine agonists eg levodopa – may potentiate effects • Oestrogens – may interfere with efficacy
Dong Quai *Angelica sinensis*	• volatile oils – eg safrole (carcinogenic) • coumarins eg bergapten- affect platelet aggregation • psoralens – photosensitisers • phytoestrogens	Diarrhoea, bleeding, photosensitivity, gynaecomastia	• Anticoagulants/ antiplatelet drugs – may potentiate effects • Oestrogens – may interfere with efficacy
Fenugreek *Trigonella foenum-graecum* seeds	• saponins eg diosgenin • alkaloids eg trigonelline • coumarins • mucilage, vitamins mild phytoestrogen, hypo-glycaemic, some effect on platelet aggregation, antacid hypocholesterolaemic	Bleeding, bruising, hypoglycaemia, allergic reactions	• Anticoagulants/ antiplatelet drugs – may potentiate effects • Antidiabetic drugs – increased hypoglycaemic effect • Oestrogens – may interfere with efficacy
Ginseng, Panax	• ginsenosides vasoconstrictor, CNS stimulant, inhibits CYP P450 2D6, immunostimulant, decreases platelet aggregation, affects HPA axis activity	insomnia, mastalgia, increased menstrual flow, tachycardia, BP fluctuations, diarrhoea, oedema, euphoria	• Anticoagulants/ antiplatelet drugs – may potentiate effects • Antidiabetic drugs – increased hypoglycaemic effect • CYP P450 2D6 substrates eg ondansetron, pethidine, clozapine – may elevate drug plasma levels • Immunosuppressants – may interfere with activity • Warfarin – may decrease efficacy
Laetrile (Apricot kernel)	• amygdalin yields – hydrocyanic acid & laetrile a dose related toxin-	*acute:* nausea, hypotension, convulsions, paralysis; *chronic:* goitre, mental retardation	• Nil known
Kava	• kavalactones (3.5% extracted in water vs 70% extracted in solvents) dopamine antagonist, CNS depressant, hepatotoxin,	*common:* gastric upset, dizziness, sedation, dry mouth, extrapyramidal, rash; *uncommon:* hepatotoxicity	• CNS depressants eg alcohol, benzodiazepines, – increased sedation • Many CYP P450 substrates (especially 2D6, 3A4, 2C19, 1A2) – elevating many drug levels eg cyclophosphamide, cyclosporine

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CAM	Constituents – Actions	Adverse Reactions	Interactions
Mexican Wild Yam *Dioscorea villosa*	Advocated as progesterone-like activity BUT some species contains • diosgenin (phytoestrogen) • DHEA • phytosterols, smooth muscle relaxant, steroid precursor	Headache, nausea, menstrual irregularities, hair loss, hirsutism, oily skin	• Oestrogens – may interfere with efficacy
Misletoe *Phoradendron species*	• phoratoxins (similar to cardiotoxin from cobra venom) smooth muscle stimulant, vasocontrictor	dose dependent BP fluctuations, bradycardia, hypovolaemia, cardiac arrest, death	• Nil known
Red clover *Trifolium pratense* flowering tops eg Promensil, Rimostil	• coumarins • flavonoids (phytoestrogens) e.g. daidzein, quercetin, • saponins, volatile oils selective oestrogen receptor modifying activity, decreases platelet aggregation, inhibits CYP P450 3A4	Headache, nausea, diarrhoea, myalgia, weight gain, menstrual irregularities	• Anticoagulants/ antiplatelet drugs – may potentiate effect • Oestrogens – may interfere with efficacy • Tamoxifen – may interfere with efficacy • CYP P450 3A4 substrates eg statins, ketoconazole, triazolam – may elevate drug plasma levels
Saw Palmetto *Serenoa repens*	• Sitosterol steroids with anti-androgenic, oestrogenic, anti-inflammatory	common – dizziness, nausea; uncommon – cholestatic hepatitis	• Anticoagulants/ antiplatelet drugs – may potentiate effect • Oestrogens – may interfere with efficacy

To prevent or minimise the occurrence of CAM-related adverse events, a suggested strategy is as follows.

- Ask your patient, using an open, non-judgemental approach, whether he/she is using CAMs.
- If so, clarify the aim of therapy e.g. general well being, disease prevention, symptom relief or treatment to change disease outcome.
- Discuss the outcomes, level of evidence and the risk-benefit of all therapy options, pharmaceuticals, CAMs, non-drug therapy and no therapy. Community based health professionals have access to the NPS Therapeutic Advice and Information Service on 1300 138 677 to assist in finding this information.

Together, make a decision for the way forward.

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Why do people use complementary and alternative therapies?

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Complementary and alternative medicines (CAM's) are widely used in the Australian community and have been the subject of a recent Senate inquiry into services and treatment options for people with cancer[1]. The report of this Inquiry accurately portrays the ideological divide between advocates of orthodox and alternative medicine as well as the structural approach to research into CAM's with its focus on definitions, classifications and demographics. To date, however, there has been little research evaluating what patients with cancer expect of CAM's.

In a cross-sectional study of patients with advanced cancer and a limited life span, we investigated the expectations of treatment, both conventional and alternative, in order to determine their perceived impact on outcome[2]. Of 149 participants, 45 (31%) believed their cancer was incurable, 61 (42%) were uncertain about curability, and 39 (27%) believed their cancer was curable. Although these findings might suggest inadequate communication, 39 (36%) of the 108 participants who believed their cancer was curable or who were uncertain about its curability acknowledged a report of incurability by their oncologists. For these participants, communication was adequate but at odds with their own beliefs. Furthermore, none of the 45 participants who believed their cancer was incurable reported that their oncologist had informed them that it was curable. These findings are consistent with a range of psychological adaptions to a life threatening illness rather than inadequate communication. Evidence to support this view is provided by the use of alternatives to conventional medical treatments by the participants and their need to have control over decisions about treatment. In this study, 33 participants were strongly committed to using alternatives to conventional medical treatment. These participants were more likely to believe their cancer was curable ($p < 0.001$) and were more likely to have a higher need for control over decisions about treatment ($p < 0.004$). Furthermore, need for control scores were highest in those participants who believed their cancer was curable or who were uncertain about curability but who acknowledged a report of incurability by their oncologist.

To date, there has been little formal evaluation of patients' expectations of having control over decisions about treatment despite the fact that autonomy and informed decision making are central planks of contemporary western bioethics and daily oncology practice. In this study, only 11% of participants were deemed to have a high need for control over treatment decisions, a figure that is supported in a study by Salkeld G et al that evaluated treatment decision making in operable colorectal cancer[3].

The overall findings of this study support the view that positive illusory attitudes and beliefs translate into actions for some patients that include a strong commitment to alternatives to conventional medical treatments. Furthermore, positive illusions can have implications for the perception of quality of life for some patients with advanced cancer[4].

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SESSION 8: LOOKING TO THE FUTURE

Future directions – A surgical perspective

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All breast cancer treatment is interdisciplinary and all physicians who treat breast cancer, surgeons included, share the same goals: early diagnosis, accurate staging, minimal local recurrence, maximal survival, and minimal treatment-related morbidity, with optimal cosmesis and quality of life. From the perspective of a surgeon, where do we stand and where are we headed?

Detection

Screening mammography has proven effective in reducing breast cancer mortality[1], and digital mammography does not yet appear more sensitive than conventional film screen techniques for cancer diagnosis. Mammography is less sensitive in younger patients and/or those with dense breast tissue, and in this setting, diagnostic and/or screening ultrasound is proving increasingly useful[2]. An extension of digital mammography, "tomosynthesis", is particularly promising[3]. MRI offers high sensitivity but low specificity[4], with frequent false-positive results, and as summarized in a recent Consensus Statement[5] appears most useful to detect occult primary disease, to monitor the response to neoadjuvant chemotherapy, to define extent of disease in patients with proven cancers, in screening very high risk populations (particularly those with deleterious *BRCA* mutations), and in those situations which remain ambiguous despite an otherwise complete evaluation by clinical exam, mammography and US. A major, and unrealized, goal for breast cancer detection is to develop diagnostic algorithms which maximize sensitivity, maximize specificity (i.e. minimize false-positive results), and control cost.

Diagnosis

Image-guided biopsy techniques, including stereotactic, US-guided, and (most recently) MRI-guided, are in general superior to surgical biopsy for virtually all breast lesions, and remain underutilized. Advantages include comparable accuracy, lower cost and (for those patients who require surgery) fewer operations[6]. The results of image guided biopsy are optimized with 11 gauge (or larger) needles, vacuum assistance, multiple samples, and clip placement to mark the biopsy site. Surgical biopsy is required whenever a core biopsy finds atypical hyperplasia, LCIS, papillary lesions, radial scar, or is discordant with the imaging characteristics of the lesion. A major, and unrealized, goal is to make a diagnosis of cancer prior to surgery whenever possible, and thereby minimize the rate of reoperation.

Surgery

The surgical treatment of breast cancer has become increasingly conservative[7], and breast conservation has proven equivalent to mastectomy in clinical trials with follow-up now exceeding 20 years[8,9]. Sentinel lymph node (SLN) biopsy is a new standard for axillary lymph node staging[10], and has proven equal or superior to axillary dissection in every aspect, including local control[11]. Major, and unrealized, goals include defining the role of SLN biopsy at each end of the disease spectrum (DCIS and inflammatory cancer), defining the prognostic significance of SLN micrometastases (and especially of isolated tumor cells, "ITC's"), defining the prognostic significance of a negative SLN (where survival should be superior to that of patients who are node-negative by conventional histopathology), and disseminating the technique of SLN biopsy (a relatively simple operation) worldwide.

Tumor ablation by in-situ techniques (either radiofrequency or cryoablation) remains a subject of active study[12]. A major, and unrealized, goal for future investigation is to prove that the benefits (avoidance of surgery on the breast) outweigh the risks (under staging by core biopsy, loss of the remaining tumor specimen, unknown margin status, and persistent scarring at the tumor site).

In the decade since the discovery of the breast cancer susceptibility genes *BRCA1/2*, testing for inherited mutations has come into widespread use; the challenge for the surgeon is to identify those patients who might be at hereditary risk and, for those who test positive, to help them weigh the pros and cons of prophylactic surgery[13]. This decision-making may be quite different for patients who have not yet developed breast cancer, compared to those who have. Prophylactic mastectomy is effective in preventing breast cancer, both for patients with high risk family history[14] and for those with proven BRCA mutations[15], but is an operation with unpredictable psychosocial sequelae[16] and should never be undertaken in haste. Prophylactic oophorectomy reduces the risk of both ovarian and breast cancer[17,18] and should be offered to all women with *BRCA1-2* mutations, especially those beyond the years of childbearing.

Radiotherapy

The role of post-mastectomy radiotherapy (RT) in reducing local recurrence (LR)[19], and perhaps enhancing survival[20,21], is well established for high-risk patients, especially those with T3 cancers and/or >3 positive axillary nodes. Post-mastectomy RT does have morbidity, and its role in patients with less advanced disease remains unclear.

The role of RT in breast-conserving surgery is clearer. For patients with DCIS, RT reduces LR by about half[22,23], but without a survival benefit. There are low-risk subsets of patients with DCIS for whom RT may be withheld[24], keeping open the option of RT used for "reconservation" if LR develops at a later date. For patients with invasive cancer, RT clearly reduces LR[7]; while no individual trial shows a survival benefit associated with this reduction in LR from RT, a recent meta-analysis[25] (comprising 13 trials and 8206 patients) suggests a survival benefit in the range of 8%.

As for surgery, breast RT is becoming more conservative. Most LR in the conserved breast develop at the original tumor site[26], suggesting that conventional RT (which treats the entire breast) could be replaced by a more limited field. Available methods include intensity-modulated external beam RT, or therapy given to the tumor bed by a) surgically-implanted catheters, b) an intracavitary balloon, or c) as a single intraoperative dose. All three of the latter methods are the subject of a prospective trial, NSABP B-39[27], which aims to determine relative value of partial- vs whole-breast RT.

Systemic therapy

Recent advances in systemic adjuvant therapy for breast cancer are among the most exciting in contemporary oncology, as treatment evolves from tamoxifen (the first targeted therapy for breast cancer) to the aromatase inhibitors (AI), and from "shotgun" chemotherapy to new classes of drugs directed at specific molecular targets. This subject is of course beyond the scope of this abstract, but deserves a caveat.

While it seems intuitive that earlier diagnosis of disease should allow more conservative treatment, in breast cancer this is not entirely the case. As both surgery and RT are becoming more conservative, systemic therapy (chemotherapy and hormonal) is becoming more "radical", with virtually every breast cancer patient (Stage 0 included) considered to be a candidate for treatment. Immense clinical trials are powered to find statistical significance for the smallest of survival benefits (1-2%), or (if no survival benefit is found) for the smallest reductions in LR, and all trialists dramatize their findings by expressing the results as a *relative* benefit rather than an *absolute* one. The greatest unmet goal for us as clinicians treating breast cancer, having given our patients the clearest possible estimate of the risks posed by their cancer and of the benefits/risks associated with each treatment, is to decide both *collectively as a profession* and *jointly with each of our patients*, exactly when a "treatment benefit" is too small to be worth pursuing.

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The new world of systemic treatments

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Significant improvements in our understanding of the molecular changes that occur in cancer cells has led to an explosion of new targets and drugs for clinical testing. These new drugs are designed to modulate, inhibit, or otherwise interfere with the function of specific molecular targets that are crucial to breast cancer development and growth. Targeted therapies are playing an increasing important role in breast cancer and are improving the clinic outcomes of women. The oestrogen receptor pathway has been the traditional therapeutic target for decades, with treatments such as ovarian ablation, tamoxifen and more recently the aromatase inhibitors.

The humanized monoclonal antibody, trastuzumab, was developed as a therapy targeted against the human epidermal growth factor receptor 2 (HER2), which is over-expressed in approximately one fourth of patients with invasive breast cancer. Randomized trials have demonstrated a significant survival benefit associated with the introduction of this agent in addition to chemotherapy in women with HER2 over-expressing metastatic breast cancer[1]. As a single agent, trastuzumab is associated with response rates of up to 34% in previously untreated, HER2 positive, metastatic disease[2]. Given the excellent activity and tolerability of trastuzumab in the metastatic setting, extensive evaluation of this agent in the adjuvant setting has been undertaken.

The early results of three of the four international adjuvant trastuzumab trials for HER2 positive early stage breast cancer were presented in May 2005. Two large American trials, the NSABP B-31 and NCCTG N9831 trials both compared the use of four cycles of standard adriamycin and cyclophosphamide chemotherapy followed by three months of paclitaxel either given on a weekly or three weekly schedule with the same chemotherapy plus trastuzumab commenced concurrently with paclitaxel and then continued as a single agent for a total duration of 12 months[3]. Together, the studies involved 3351 patients and the data presented was based on a mean follow-up of only 2 years. The joint analysis showed the addition of trastuzumab reduced the risk of breast cancer recurrence by 52% (hazard ratio, 0.48; 2*P* value=$3x10^{-12}$). This translated into substantial improvements in estimated 3- and 4-year DFS (see Table 1). Despite the short follow-up, the pooled data also showed an improvement in overall survival (hazard ratio, 0.67; 2*P* = .015)[3].

Table 1 Estimated Recurrence Risk and Overall Survival in Adjuvant Trastuzumab Trials: Pooled NSABP + NCCTG Data

	AC → Paclitaxel	AC → Paclitaxel + trastuzumab
3yr estimated DFS	75%	87%
4yr estimated DFS	67%	85%
3yr estimated OS	92%	94%
4yr estimated OS	87%	91%

However, the survival benefits associated with trastuzumab appear to come at the price of an increase in the risk of clinically-apparent heart failure. The risk of cardiac events was 4% among those treated with chemotherapy and trastuzumab given concurrently compared with 0.6% for those given chemotherapy alone. There are also data suggesting that older patients and those patients with borderline normal LVEF at baseline may be at greater risk for cardiac events[3].

The HERA trial randomised patients with HER2 positive breast cancer to receive either placebo, or 1 or 2 years of trastuzumab in the adjuvant setting[4]. In contrast to the American trials, patients were enrolled in the HERA Trial after completion of adjuvant chemotherapy and radiation treatment (if given). Patients received at least 4 cycles of a standard but not specified adjuvant chemotherapy regimen, with 68% of eligible patients having received anthracycline-based chemotherapy and 25% received anthracycline- and taxane-based chemotherapy. Trastuzumab was given every 3 weeks (6 mg/kg) in contrast to the weekly (2-mg/kg) regimen in the American trials. The early results comparing placebo with one year of trastuzumab have been presented and the results of the optimal treatment duration (one versus two years) are expected in 2008. At a median follow up of 1 year, the addition of trastuzumab was associated with a 46% reduction the risk of breast cancer recurrence (hazard ratio, 0.54; *P*<0.0001). The estimated 2-year DFS for chemotherapy alone was 77% vs 86% with trastuzumab. At this very early follow up, no overall survival has been seen. Cardiac toxicity was significantly less with trastuzumab given in sequence after chemotherapy with an event rate of 0.5% compared with 0% in the placebo arm[4]. Thus, the addition of trastuzumab into the adjuvant treatment algorithm for HER2 positive breast cancer represents an exciting and significant step forward for targeted therapies in improving breast cancer survival.

Targeting angiogenesis has now shown survival benefits for patients with metastatic breast cancer. The Eastern Cooperative Oncology Group Trial, E2100 was a randomized study comparing paclitaxel alone vs paclitaxel plus bevacizumab as first-line chemotherapy for patients with locally recurrent or metastatic disease[5]. Bevacizumab is a humanized

monoclonal antibody directed against the vascular endothelial growth factor (VEGF) receptor; it is believed to work by inhibiting vascular proliferation in tumours. Patients had received no prior chemotherapy for metastatic disease, and had at least a 12-month disease-free interval since receiving a taxane in the adjuvant setting. Objective overall response rates were 14.2% for paclitaxel alone and 28.2% for paclitaxel plus bevacizumab (P<0.0001). Progression-free survival was superior for patients receiving bevacizumab plus paclitaxel, with a median of 11 months for the combination vs 6.1 months for paclitaxel alone (log rank test P<0.001). Overall survival was also improved with the addition of bevacizumab, although the medians have not been reached in either arm (hazard ratio, 0.67, P = 0.01)[5]. Confirmatory studies are needed in the metastatic setting in combination with chemotherapy, hormonal therapy and other biologic agents and plans for adjuvant trials are underway.

With the rapidly increasing number of new drugs in development and the huge expense required for bringing a drug to market it is paramount to identify patient subpopulations that are most likely to benefit from a new targeted therapy. Genomic, proteomic and pharmacogenetic technologies are beginning to play an important role in this process. A collaborative approach between basic scientists, clinicians and industry will continue to solidify targeted therapy as the way of the future!

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Biomarkers and molecular markers for evaluation of the primary tumor. Ductal lavage – update on results

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NOTES

With the current availability of Tamoxifen as a chemopreventive agent and with the increasing emphasis on early breast cancer detection and prevention, more women seek consultation to determine their risk for breast cancer. However, in the absence of any detectable breast lesion, clinically and mammographically, only a few women may volunteer to have their breasts sampled by surgical biopsy for risk assessment. Other non-surgical procedures include fine needle aspiration biopsy (FNAB), nipple aspirate fluid (NAF) and the recently introduced procedure, ductal lavage. These techniques may provide better alternatives.

Based on the minimally invasive procedures are capable of recruiting cellular material for cytomorphologic interpretation as well as biomarker studies. Limited reports in the literature have demonstrated the value of cytomorphology as a risk predictor in FNAB and NAF samples. Wrensch et al used traditional morphology to assess the presence as absence of atypia in the samples obtained from NAF.

In a prospective study with cytologic-histologic correlation using mammographically directed FNAB and the follow up needle localization excisional biopsy were able to define the cytomorphology of high-risk proliferative breast disease. We developed a semiquantitative cytologic grading system, which allowed us to stratify the spectrum of high-risk proliferative breast disease and to distinguish between hyperplasia and neoplasia. This grading system has remained rather unrecognized among the pathology community. However, as the only prospective study with appropriate cytologic histologic correlation, this system has gained acceptance among oncologists and researchers. This grading system recognized as "Masood Cytology Index" has been used in several National Cancer Institute Funded Projects and has demonstrated its value as a breast cancer predictor. As a potential surrogate endpoint biomarker, this index has also been used in the monitoring of the effect of therapy.

Recently in a report by Bean et al, the authors studied the pattern of distribution of retinoic acid receptor-beta (RAR beta2P2) promoter methylation in random periareolar fine needle aspiration using Masood Cytology Index. Results from the study indicated that RAR beta2p2 promoter shows a positive association with increasing cytologic abnormality. The highest level of methylation at M3 and M4 (50%) has observed with cytology score as high as 14-15 (atypical ductal hyperplasia). This study is the reflection of the validity of Masood Cytology Index, which can stratify low-grade proliferation from high-grade proliferation. This is a promising study, which may trigger more interest among other investigators to further study the potential use of this approach in ductal lavage studies.

Ductal lavage is a novel technique, which inserts a microcatheter into individual breast ducts to collect cellular material for cytologic evaluation. The devices used in ductal lavage are FDA-approved and have been cleared for use and marketing in the United States.

The results of a multi-center clinical study on ductal lavage has been recently published. In this study, five hundred and seven high-risk women were enrolled at nineteen centers. The participants had no abnormality clinically and mammographically within the twelve months prior to enrollment. The inclusion criteria were one or more of the following: previous history of breast cancer, five-year Gail risks over 1.7%, and positivity for BRCA1 and/or BRCA2. The participants underwent nipple aspirate fluid and ductal lavage. The cytologic samples were interpreted as inadequate, benign, and mildly atypical, markedly atypical, and malignant. Abnormal cells were identified in 24% of the subjects who underwent ductal lavage. The cellularity was significantly higher in ductal lavage specimens compared to nipple aspirate fluid. Only 27% of the samples collected through nipple aspiration were adequate. By contrast, the adequacy rate for ductal lavage was 78%. The ductal lavage procedure was successful in 84% of the cases. It was also found that ductal lavage is a safe and well-tolerated procedure. In a follow up study, recommendations have been provided for the clinical management of patients who undergo ductal lavage.

In our limited experience, we have found that ductal lavage is an effective means to sample cells from the breast ductal system. After the necessary cytomorphologic standardization and correlation studies, this procedure can be a powerful tool for early breast cancer detection and risk assessment. In conjunction with the newly identified genetic markers, ductal lavage has the potential of identifying early breast cancers before any mammographic changes occur.

The most exciting application of ductal lavage is the opportunity to study the genetic alterations associated with breast cancer. Currently, there is almost no information as to the earliest genetic changes, which start in a cell on the journey towards malignancy. It is logical to assume that at least some of the genetic changes, which have been observed, in invasive breast cancers are present in the early stages before phenotypic malignancy. A demonstration of somatic genetic abnormalities in breast epithelial cells would provide crucial leads to genes which deserve to be studied as molecular predictors of breast cancer risk in women who do not yet have the disease.

NOTES

Currently, ductal lavage is a procedure with great potentiality, which deserves cooperation of clinicians, researchers and high-risk individuals to further validate its application in both clinical practice as well as breast cancer research. Ductal lavage cannot be constructed as a substitute for clinical exam and mammography and is not viewed as a screening tool for the general population. In my opinion, ductal lavage is another piece of the puzzle for an individualized risk assessment and is a vehicle to study the cells at the molecular level.

The nipple is distinctively positioned to provide unique opportunities to study the pattern of presentations of breast cancer precursors. Intraductal approach via nipple fluid aspiration and ductal lavage allows us to study the spectrum of morphologic changes and pattern of gene expression of breast epithelial cells. Ductoscopy allows direct visual access to the ductal system of the breast through nipple orifice exploration. Ductography captures the earliest anatomical changes associated with malignancy. Access to the breast epithelial cells and their surrounding environment, via the nipple, coupled with the use of emerging new technologies has incredible potentiality for an improved understanding of the biology of breast cancer precursors.

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Potential future developments for breast imaging

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NOTES

Mammography is the only proven breast cancer screening tool, but is quite imperfect. There is always high interest in either replacing or supplementing mammography. Dr Berg has shown that mammography's performance is inversely proportional to the mammographic density of the breast. (Table 1) Based upon this data, a subgroup of women who have dense breast tissue on mammograms has been targeted for further evaluation.

	Sensitivity All CA	Sensitivity IDC	Sensitivity ILC	Sensitivity DCIS
Homogeneously dense	45%	60%	11%	25%
Heterogeneously dense	70%	86%	36%	64%
Scattered densities	79%	89%	60%	60%
Entirely fatty	100%	100%	100%	100%

An important point to remember when trying to develop or evaluate any modality's ability to detect breast cancer is that breast cancer is heterogeneous – not only from one nodule to another, but even within an individual nodule. This heterogeneous population of malignant breast lesions can be illustrated as a spectrum from spiculated lesions at one end to circumscribed lesions at the other end of the spectrum. In the middle lie lesions that are internally heterogeneous – that have some features of both spiculated and circumscribed lesions. It is important to realize that key histologic, physical, chemical, and even electrical properties not only differ between spiculated and circumscribed lesions, but are often opposite. A successful imaging tool for breast cancer must be able to detect both circumscribed and spiculated lesions with high sensitivity. It has taken decades for us as mammographers and sonographers to figure out how to achieve this. Using mammography and sonography as a template, we are learning to achieve this more rapidly in MRI. Thus, at his point, the big 3 – mammography, ultrasound, and MRI – all have demonstrated the potential to "diagnose" both spiculated and circumscribed breast cancers with a high sensitivity. This is not at all the same as demonstrating high efficacy of ultrasound and MRI for breast cancer screening. In fact, ongoing studies by the ACR Imaging Network (ACRIN) are being performed to assess the efficacy of MRI (ACRIN 6667) and bilateral whole breast ultrasound (ACRIN 6666) for breast cancer screening in subpopulations of women with dense breast tissue on mammography and who are also at high risk for breast cancer. These subpopulations were chosen because: 1) such subgroups are where mammography tends to fail, and 2) fewer study patients would be necessary to demonstrate efficacy with adequate statistical power. The ACRIN 6667 study of MRI has been closed, but the final results have not yet been analyzed or published. The ACRIN 6666 trial is still open, but accrual will likely be complete by the end of 2005.

Many additional modalities are being evaluated as breast cancer screening tools. These include: optical scanning, thermography, impedance imaging, elastography, acoustic vibratory imaging, mechanical palpagraphy, and tactile imaging among others. The problem with many of these additional imaging modalities is that they are target primarily at one end of the malignant spectrum or the other. Most of these modalities are far more effective for either circumscribed lesions or spiculated lesions, but not necessarily for both. Thus, they are disadvantaged as compared to the big 3 – mammography, ultrasound, and MRI – for detecting breast cancers.

Circumscribed carcinomas tend to be high grade invasive ductal carcinomas, highly cellular, have an extracellular matrix composed primarily of hyaluronic acid, and tend to incite a lympho-plasmacytic host response. Such lesions are high in water content, relatively soft, and have lower electrical impedance. They also tend to be much more vascular. The high tumor cellularity results in more neo-angiogenesis and the lymphocytic and plasmacytic host response also results in inflammatory hyperemia. Thus, modalities such as Doppler (with and without contrast), optical scanning and thermography, which target vascularity, are most effective for high grade circumscribed carcinomas. Impedance imaging also is more effective for circumscribed lesions. Such modalities are less effective at detecting lesions that lie at the spiculated end of the spectrum.

Spiculated malignant breast lesions tend to demonstrate much lower tumor cellularity, tend to have an extracellular matrix that contains more collagen and less hyaluronic acid, incite primarily a desmoplastic fibroelastotic host response. Such lesions are much lower in water content, are harder than circumscribed lesions, and incite relatively less neovascularity. Modalities that assess primarily "stiffness", such as ultrasound or MR elastography, mechanical palpagraphy, tactile mapping, and acoustic vibratory imaging are quite effective at detecting lesions at the spiculated end of the spectrum. However, such modalities are much less effective at detecting lesions that lie at the circumscribed end of the spectrum.

Current "Big 3" modalities are also undergoing improvements. Mammographic improvements include full-field digital, CAD, dual energy digital mammography and tomosynthesis with and without contrast enhancement. CAD is now well-accepted in the US, but dual energy

and tomosynthesis are still considered investigational. Sonographic developments include a variety of automated whole breast reflective sonography equipment, whole breast transmission and speed of sound equipment, and integrated full-field digital mammography – whole breast digital ultrasound equipment. Several different companies are developing ultrasound CAD, which is still considered investigational. The available ultrasound CAD programs all appear to look only at the hypoechoic part of sonographic lesions, which represents a significant disadvantage over experienced sonographers, who incorporate the hyperechoic parts of the lesion and host response into the interpretive algorithm. Ultrasound contrast agents are also being evaluated, but like unenhanced Doppler, seem to be more effective for circumscribed highly cellular lesions than they are for spiculated lesions. Most of the ultrasound developments are geared toward automated scanning with CAD to try to overcome the operator dependence of ultrasound and to try to work around the shortage personnel who are qualified to perform hand-held bilateral whole breast screening ultrasound.

MRI developments include improved spatial resolution and the ability to achieve both high spatial resolution and good temporal resolution for dynamic imaging in the same patient. MRI CAD is also being developed. The ability to perform MRI guided biopsies has been greatly improved. MRI, together with "second-look" ultrasound and either ultrasound guided or MRI guided mapping biopsies is becoming the standard of care for pre-operative staging of cancers in patients who desire breast conserving surgical treatment.

Contrast enhanced x-ray CT certainly could demonstrate both adequate spatial and contrast resolution for breast diagnosis, but delivers an unacceptably high radiation dose. Thus, CT is unlikely to supplant MRI and ultrasound in breast diagnosis and screening.

Of the "Big 3" developments, the combined full-field digital mammography and automated whole breast ultrasound seem to be the most compelling from an economic and manpower point of view. A single room, a single machine containing both digital mammography and breast ultrasound, and a single technologist are all that are required. Full-field digital mammography and whole breast ultrasound can be accomplished in a single patient visit. The mammogram and ultrasound are automatically co-registered, so there will never be a question mammographic-sonographic correlation. Unlike any other stand-alone imaging modality, the automatic co-registration of mammography and ultrasound promises to decrease callbacks diagnostic ultrasound to evaluated soft tissue abnormalities. When mammographic densities are caused by cysts or hyperechoic fibrous tissues, callback should not be necessary. All other modalities that are not co-registered with mammography are likely to increase callbacks. CAD will be available as a "second reader" for both the full-field digital mammogram and the whole breast ultrasound.

Modalities other than the "Big 3" can be classified into general groups: stiffness imaging, optical imaging, thermal imaging, impedance imaging, and molecular imaging. Molecular imaging contrast agents can be used in combination with other modalities – in particular, with optical imaging.

Modalities that assess "stiffness" will be more effective at detecting lesions that contain primarily a collagenous stroma and elicit pronounced desmoplasia – i.e. malignant lesions that lie at the spiculated end of the spectrum. Modalities for assessment of stiffness include acoustic vibrational power Doppler, ultrasound and MR elastography, tactile mapping of the breast, and mechanical palpation (Ultra-Touch). In general, acoustic vibrational power Doppler, and both ultrasound and MR elastography are designed to be used by breast imagers. Tactile mapping and Ultrasound are designed to aid primary care physicians in performing the physical exam.

Optical imaging methods include diffusion imaging and optical coherence tomography. Both use light at near-infrared wavelengths that tend to be absorbed by hemoglobin, particularly deoxygenated hemoglobin. Thus, optical imaging tests work best for vascular lesions, lesions that tend to lie at the circumscribed end of the malignant spectrum. The DOBI light scan uses a diffusion form of optical scanning. Several companies are developing laser CT, using a laser at a near infrared wavelength. The spatial resolution of laser CT has been disappointing, but laser CT can be used with molecular imaging contrast agents that absorb light at a wavelength near that of infrared promise to greatly improve spatial resolution. Laser CT with or without molecular contrast agents is targeted at dedicated breast imagers, but diffusion optical scanning has been targeted at primary care physicians.

In the strictest sense, thermal imaging is merely a variant of optical imaging. Thermal imaging detects heat, which varies directly with vascularity. Like optical imaging, it tends to be most effective for vascular lesions that lie at the circumscribed end of the malignant spectrum.

Impedance scanning is based upon the fact that many carcinomas transmit electricity with lower impedance than do normal breast tissues. This is a reflection of cellularity. Cells, which are water and electrolyte rich, transmit electricity with lower impedance than do hypocellular stromal tissues such as fat or fibrous tissue. However, not all breast carcinomas are highly cellular. Spiculated lesions are paucicellular, have abundant collagenous stroma, and incite fibroelastotic desmoplasia and therefore may not demonstrate decreased impedance. It would be expected that impedance imaging would be more effective at detecting highly cellular circumscribed lesions.

Both thermography and impedance imaging are targeted at primary care physicians rather than breast imagers.

Many of the "new" developments are simply older technologies that are being reevaluated because of improvements in digital computing that allow the data collected to be more effectively analyzed and displayed. In a sense, "what goes around comes around." Whole breast dedicated breast ultrasound machines were the first breast ultrasound machines. Higher frequencies, computed tomography techniques, and increased computational power and speed merit another look. Optical scanning is the newest iteration of "diaphonographic" light scanning of the breast. Thermography has been around for decades, at both infrared and microwave wavelengths, but again improved depth resolution and color displays warrant further evaluation. Palpation was the original method of evaluating the breast. Digital means of assessing stiffness merely represent digitally augmented of palpation.

For the time being, all modalities other than the "big 3" - mammography, hand held ultrasound, and contrast enhanced MRI - should be considered investigational.

It should be apparent from the above discussion that breast imaging modalities that are being evaluated are myriad. Many of the niche modalities are theoretically disadvantaged because they are designed to detect one end of the spectrum far more effectively than the opposite end of the spectrum. This means that the odds are stacked against these modalities when they are used alone.However, the reason that all of these modalities are being evaluated is that mammography is far from perfect. Mammography works as well as it does today because we have learned its weakness and how to compensate for these by correlating clinical, sonographic, and occasionally MRI findings when necessary. On a theoretical basis, combining an investigational modality that excels at detecting circumscribed malignant lesions with a modality that excels at detecting spiculated lesions should compensate for the weakness of each.Thus, combining impedance scanning (which is theoretically better at detecting circumscribed high grade carcinomas) with mechanical digital palpation (Ultratouch, which is theoretically better for spiculated low grade carcinomas) might achieve the desired sensitivity for the primary care physician. Optical scanning might be combined with elastography to achieve the desired sensitivity for breast imagers. The odds might be against these modalities right now, but perhaps it is best to "never say never."

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Most of the information on new technology comes from web pages.

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POSTERS

G3BP2 as a tumour associated antigen in breast cancer

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Breast cancer is the leading cause of mortality in Australian women. Treatment for early stage disease involves a combination of surgery and chemo-radiotherapy with good outcomes. However, prognosis for advanced breast cancer is poor and there is a clear need for the development of new therapies to improve outcomes for these patients.

Identifying new tumour associated antigens (TAA) for breast cancer is essential for the progression of dendritic cell (DC) immunotherapy as a treatment for this disease. DC loaded with TAA are able to generate effective anti-cancer responses and several phase 1 clinical studies (melanoma, multiple myeloma and prostate cancer) have reported complete and partial remissions in patients with advanced disease.

G3BP2 (ras-GTPase-Activating Protein SH3-Domain-Binding Protein) was first identified as a novel protein over-expressed in breast cancers but not expressed in normal breast tissue. It has been implicated in signal transduction and RNA metabolism pathways that control cell proliferation and survival. Due to its selective tissue expression, G3BP is a promising candidate as a TAA to use as a target for cytotoxic T lymphocytes (CTL).

We have identified four A2 restricted epitopes within the G3BP2 molecule and demonstrated that these bind to the HLA-A201 molecule. We have been able to elicit a CTL response towards one of the four peptides on ELISPOT. Several polyclonal cell lines from this CTL pool have demonstrated cytotoxic activity towards T2 cells bearing a G3BP2 peptide. Further work is being done to develop single cell clones with cytotoxic activity towards breast cancer cell lines.

Evaluation of response to pre-operative chemotherapy for locally advanced breast cancer: A comparison of conventional methods with PET scan and biological markers

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Background

The pathological response remains the best predictor of outcome in women treated with pre-operative chemotherapy for locally advanced breast cancer. Women undergoing pre-operative chemotherapy are assessed with biopsy, mammogram, ultrasound, positron emission tomography (PET), and biological markers on tissue and blood pre, during and after chemotherapy.

Methods

20 patients enrolled after screening to exclude distant metastases and inflammatory breast cancer. Patients are randomized to receive FEC100 x4 or Docetaxel x4, then crossed over following the interim assessment. 10 patients have completed all 8 cycles of chemotherapy, 9 have undergone surgery.

Results

All patients had markedly positive PET scans pre-treatment. Standardized uptake value (SUV) median 6.48 with range 1.76 – 14.9. All patients have responded to chemotherapy. Of the 9 patients completing surgery, 2 pts had a complete pathological response, and 2 patients had minimal microscopic residual disease with negative nodes.

After 1st 4 cycles of chemotherapy

	Clinical N = 14	Mammogram N = 14	Ultrasound N = 14	PET N = 14
Complete Response	3 (21%)	2 (14%)	2 (14%)	4 (29%)
Major/Partial Response	5 (36%)*	2 (14%)*	3 (22%)*	2 (14%)**
Others (SD, PD)	6 (43%)	10 (70%)	9 (64%)	8 (57%)

* – > 50% reduction in largest diameter
** – >50% reduction in SUV

Path Response Post 8 cycles (n =9)

PET post 4 cycles	Complete	Major	Minor
CR/MR	2	1	3
SD	0	1	2

Conclusions

PET is a promising tool in predicting response to neoadjuvant chemotherapy.

Carcinoma arising in fibroadenomas

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Background

Fibroadenomas of the breast are a common cause of a palpable lump in young women, and a common incidental finding on screening mammography.

The usual proliferative and malignant changes can occur within a fibroadenoma: e.g. hyperplasia with or without atypia, in situ and invasive malignancy. The risk of developing a breast cancer within a fibroadenoma is low and equivalent to that of glandular tissue elsewhere in the same breast. There is some increased risk of malignancy associated with fibroadenomas showing histologic changes of "complex fibroadenoma", or in cases where there is a significant family history of breast carcinoma. Occasionally metastases or other rare cancers can be found in a fibroadenoma.

The radiological diagnosis of carcinoma within a fibroadenoma is based on the usual imaging findings, such as change in shape or size, irregular margins or suspicious calcifications. The methods used for diagnosis, and the treatment approaches to malignancy within fibroadenomas are the same as for other breast cancers.

In the screening program, if fibroadenomas are typical on mammography, further investigation is not required and normal re-screening is recommended. When there are atypical features, assessment using the triple test approach is needed to establish an accurate diagnosis.

Case Reports

Two case reports are presented of fibroadenoma associated with invasive and in-situ ductal carcinoma, diagnosed preoperatively by core biopsy, following suspicious imaging findings.

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A 'low risk' (probably benign) symptomatic breast clinic: Reason for referral from primary care

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Background and purpose

The NSW Breast Cancer Institute (BCI) has established a 'low risk' breast clinic which supports general practitioners (GPs) in the management of women with breast problems that are not considered to be suspicious ("probably benign"). Women are triaged to this clinic according to information provided in the referral letter including the results of any imaging and biopsies where available. This study explores the reasons why patients are referred to a specialist breast clinic despite the "low risk" findings in initial investigations.

Methods

Medical records of 210 consecutive new patient referrals were reviewed to determine patient demographics, source of referral, the main reason for referral and the final diagnosis. Data were analysed to determine the distribution of these variables.

Results

Of the 210 subjects all (but 1) were women and 95% were referred by general practitioners. Subjects' age ranged from 12 to 87 years with an average age of 42.

The most common reasons for referral and final diagnoses are shown in Table 1. Most patients had benign findings, with only three patients (1.4%) being found to have a malignancy. The main reason for referral (37.6%) was 'breast lump'. In this subgroup only 68% were diagnosed as having a definite palpable lesion following assessment (Table 2).

The second most common reason for referral (25.7%) was the presence of an image-detected ('screen-detected') abnormality as an incidental finding on breast imaging and unrelated to the clinical findings or symptom.

Conclusions

We have identified two issues not previously documented in published work. First, about one third of patients referred with a 'breast lump' were found not to have a palpable finding. Second, many women are referred to our specialist breast clinic for management of benign image- or screen-detected lesions unrelated to symptoms. Both issues warrant further evaluation to ascertain whether they represent areas of need for GP support and education, or whether other underlying factors exist (such as ambiguous or inconclusive imaging reports).

A model of multidisciplinary breast cancer care

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Background

Patients with breast cancer have a better outcome when they are treated by clinicians who have a large breast cancer caseload.[1] Such clinicians often work in specialised breast units in multidisciplinary teams with input from clinicians from other disciplines.

Multidisciplinary breast cancer care has evolved because of the changes in focus of breast cancer treatment.[2] With the advent of breast conservation, there has been a need for surgeons treating breast cancer to work closely with pathologists and radiation oncologists. With the increasing use of adjuvant chemotherapy and hormone therapy, the role of the medical oncologist has also increased. A high degree of communication among the specialities is now required to deliver coordinated patient care. While the concept of 'multidisciplinary care' is now generally accepted as the 'ideal' way of treating breast cancer, there are many diverse models of such care and many barriers to setting up this style of clinic.

The model

We present a model of multidisciplinary care that has evolved since 1995 at the NSW Breast Cancer Institute in Australia. Essential elements of the model include:

1. A patient-centred approach to care
2. A dedicated multidisciplinary team
3. Standardised, documented procedures and protocols
4. A purpose-designed facility
5. The use of information technology systems
6. Research, evaluation and education

We describe how our clinic works, addressing each of these areas. We present a model of multidisciplinary case conferencing that includes 'interdisciplinary' as well as multidisciplinary discussion. This allows comprehensive consideration of each case pre- and post-operatively.

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Breast intraoperative ultrasound for impalpable lesions

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Background and purpose

Preoperative hookwire localizations are usually used to guide excision of subclinical breast lesions. These can be time-consuming, require coordination of patient, radiologist and ultrasonographer and may be very distressing for patients, especially if the localization is difficult. With the advent of high-resolution portable ultrasound machines, these localizations can be performed in the operating theatre. This presentation describes a simple method for such localizations.

Methods

From June 2003 to July 2005, 236 women with 247 subclinical breast lesions underwent intraoperative ultrasound-guided excisions. Ultrasonography was performed using a 25-mm, broadband (10-5 MHz) linear array hockey stick transducer with a Sonosite Titan portable ultrasound system. The ultrasound probe and lead were covered in a sterile plastic sheath. Sterile gel was placed inside the sheath and on the skin over the predicted location of the lesion. A clear, sterile plastic drape was placed over the operating panel of the ultrasound machine to enable machine use intraoperatively by the scrubbed ultrasonographer. After locating the lesion, a 23-G needle was passed into it and the exact location of the lesion was marked on the skin. The lesion was removed and checked with specimen ultrasonography.

Results

The relevant lesions were removed in all patients. In a previous cohort of 100 patients undergoing preoperative ultrasound-directed hookwire localizations, three lesions were missed, either due to poor positioning or displacement of the hookwire.

Conclusion

The removal of impalpable breast lesions using intraoperative breast ultrasound is reliable, rapid and relatively inexpensive.

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Assessment of adipocytes or liposarcoma in phyllodes tumour

A case report and review of the literature

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Phyllodes tumour of the breast previously called cystosarcoma phyllodes[1] is now established as a fibroepithelial neoplasm and is graded as benign, borderline or malignant depending on the stromal characteristics.

An excision of a lump from the left breast from a seventy seven year old female was sent for histopathologic examination, which showed a malignant phyllodes tumour with adipocytes in the stroma in addition to atypical ductal hyperplasia. A core biopsy done prior to this in another laboratory revealed liposarcomatous foci. In view of this subsequent further levels carried out revealed similar foci.

This illustrates the need to carefully appraise the morphological findings in the evaluation of phyllodes tumours. Malignant heterologous elements if identified even focally is an important prognostic indicater[2].

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The diagnosis of phyllodes tumours. Is it a fibroadenoma variant? A review of 84 cases.

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Background and purpose

Phyllodes tumours are uncommon fibroepithelial breast tumours which comprise approximately 2% of malignant and potentially malignant (ie non-invasive) neoplasms in our Clinic. Histologically they are classified as benign, intermediate or malignant. At presentation they are often difficult to distinguish from fibroadenomas. The purpose of this study was to review a large series of these tumours and identify features which suggest a "phyllodes".

Methods

During the period January 1988 to January 2004, 84 phyllodes tumours were detected in 81 women, concurrently with 3580 invasive and non-invasive breast cancers. The clinical records and imaging for the visit at which the phyllodes was diagnosed and for any previous visits, were studied. All the imaging was reviewed by one radiologist (AP).

Results

Almost all of the tumours were palpable and most (49%) occurred in women aged 40 to 49 years. 6% of the tumours were malignant. Radiologically, the findings were similar to fibroadenomas, and malignant phyllodes were very similar to benign. Fine needle aspiration cytology was of limited value (only 22% suggested phyllodes). Core biopsy was more reliable (65% positive). Both tests were more reliable in smaller tumours, suggesting the number of cores should be increased in larger tumours.

Whether the diagnosis was made on initial presentation (60%) or at a later visit, the median pathological size at diagnosis was the same (28mm).

All the phyllodes tumours grew, and most grew much faster than the 18%[1] of fibroadenomas which grow. Intermediate and malignant phyllodes grew faster than benign phyllodes. Whole breast ultrasound demonstrated fibroadenomas in 31% of women with phyllodes tumours.

Conclusions

All fibroadenomas need follow up to determine the rate of growth if any. Observation of a rapid increase in size is useful in the diagnosis of phyllodes. Absolute size has an influence on when the diagnosis of "phyllodes" is made. Mammography, ultrasound and cytology are of limited value in the differentiation of phyllodes from fibroadenoma, and of malignant from benign phyllodes. 31% of phyllodes tumours occur concurrently with one or more fibroadenomas, suggesting a relationship.

Reference

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The diagnosis of breast cancer in women younger than 40

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(published in *The Breast* (2004) 13,297-306)

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Background and purpose

6.5% of breast cancers are diagnosed in women under 40 years. There is no general agreement about the management of high risk women in this group. The purpose of this study was to examine how diagnosing breast cancer is different in young women.

Methods

From February 1992 to February 2002, 239 cancers were studied in women under the age of 40 years. Records for these women were compared with 2101 women aged 40 and over with breast cancer seen concurrently.

Results

Mammography was less likely to show an abnormality than in older women and the abnormality was less likely to be called "suspicious" or "malignant". Over 75% of the women under forty had dense or extremely dense breasts, and mammography performed poorly in this group. Multifocality was poorly detected on mammography. In twelve cases mammography was positive and ultrasound was negative (mostly calcified DCIS).

Ultrasound detected abnormalities more reliably than mammography, but the findings were more likely to be considered benign than in older women. Ultrasound was useful for predicting ultimate tumour size and for detecting multifocality. A subgroup of cancers was indistinguishable from fibroadenomas on ultrasound.

Fine needle aspiration cytology and core biopsy were reliable.

Invasive ductal cancer was proportionally more common and lobular and tubular cancers were relatively rare.

For symptomatic women only, the proportion of breast malignancies under 10mm was similar in the two age groups, but the younger group had more poorly differentiated tumours[1].

Conclusions

Diagnosing breast cancer in women younger than 40 is challenging, but follows the same general principles as in the older woman. If ultrasound alone was used, then eighteen cases would not have been detected. Cytology or core histology is essential in this age group. This includes the many lesions considered benign on radiology. The routine use of ultrasound in women with dense breasts in this age group should be encouraged. Whole breast ultrasound was also valuable in assessing the size of the tumour and multifocality.

Reference

1. Colleoni M, Rotmensz N, Robertson C et al. Very young women (<35 years) with operable breast cancer: features of disease at presentation. *Ann Oncol* 2002;13:273-9.

Do radiologists vary in accuracy when reporting mammography according to BI-RADS® assessment categories?

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Background and purpose

The American College of Radiology (ACR) advocates the Breast Imaging Reporting and Data System (BI-RADS®)[1], a standardised approach for reporting which, among possible advantages, could allow better comparison of diagnostic series and create a universal system for reporting breast imaging. There is an assumption that such standardisation may establish category-specific measures of accuracy that are widely applicable, but this has not been well evaluated. We studied the reporting of mammograms according to BI-RADS® assessment categories by a panel of breast radiologists to assess the extent of variability in interpretation and accuracy. This may assist judgment of how 'transferable' BI-RADS® is for reporting breast imaging.

Methods

Twelve radiologists experienced in mammography reported a study set of 50 cases, which included 29 cancers and 21 benign lesions. Radiologists were required to report according to BI-RADS categories based on the ACR criteria. Film reading was performed in a blinded manner, without knowledge of the nature or frequency of lesions in the set. Measures of accuracy (sensitivity, specificity, positive predictive value) for BI-RADS categories were calculated for all radiologists.

Results

Data are presented for all 12 radiologists (Rad 1-Rad 12) in Table 1 and Table 2. When R2 vs R3-4-5 cut-off is used to categorise results, average sensitivity was 92.8 % (range 86.2-100) and average specificity was 35.3 % (range 4-57). Average PPV per category was 21.3% (range 0-33) for R2, 50.3% (range 11-71) for R3, 60.7% (range 0-100) for R4a, 74.4% (range 62-100) for R4b, 73.8% (range 60-100) for R4c and 87.3% (range 66-100) for R5.

Conclusions

Our study shows marked variations amongst radiologists in measures of accuracy when classifying lesions according to BI-RADS assessment categories. This may be partially reduced with appropriate training[2]. We do not question the potential advantages of standardising reporting, but recommend better evaluation and highlight potential challenges in order to guide implementation of standardised reporting systems.

References

1 www.acr.org.

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Florence-Sydney breast biopsy study: Sensitivity of ultrasound-guided versus freehand fine needle biopsy of palpable breast cancer[1]

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Background and purpose

Fine needle aspiration biopsy (FNAB) is widely used in the diagnosis of breast cancer. It is unknown whether, for palpable cancers, ultrasound-guided FNAB is more accurate than freehand FNAB, and practice varies between physicians, services and countries.

Methods

From consecutive women attending a cancer centre in Florence, we prospectively recruited subjects who had a definitely palpable lump which was solid on ultrasound and suspicious of malignancy (N=102). All subjects were investigated using both ultrasound-guided and freehand FNAB (one aspirate with each method). Radiologists skilled in both sampling techniques performed all clinical examinations and aspirations, and for each subject the same radiologist obtained both FNAB samples. Sequence of aspiration method was randomised. Cytological interpretation was blinded to method of sampling. Comparative sensitivity (and insufficiency) for FNAB using the two methods was calculated in all cancers (N= 97).

Results

Data are presented in Table 1: ultrasound-guided FNAB resulted in 13.6% (5–22%) less insufficient aspirates than freehand FNAB (x^2 = 7.58; p= 0.006). When insufficient aspirates are included and considered as negative, ultrasound-guided FNAB has a 14.6% (5.8–23%) or a 16.5% (7.6–25.4%) significantly better sensitivity than freehand FNAB. When insufficient aspirates are excluded from the analysis, ultrasound-guided FNAB has a 1.4% (-1.2 to 3.9%) or a 2.6% (-2.5 to 7.8%) higher sensitivity than freehand FNAB, but this difference in sensitivity is not statistically significant.

Conclusions

Our data suggest that ultrasound-guided FNAB has better sensitivity than freehand FNAB in palpable breast cancer, which is predominantly an effect of a significant reduction in insufficient aspirates, but in part an effect of 'upgrading' cytological classification of cancers.

Reference

1 Houssami N, Ciatto S *et al.* Florence-Sydney Breast Biopsy Study: sensitivity of ultrasound-guided versus freehand fine needle biopsy of palpable breast cancer. *Breast Cancer Research & Treatment* 2005; 89: 55-59.

Review of complex breast cysts: Implications for cancer detection and clinical practice[1]

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Background and purpose

The use of ultrasound in breast diagnosis has resulted in the increasing identification of incidental benign-appearing lesions, of which complex (or atypical) breast cysts are frequently reported. Using Australian data we estimate that complex breast cysts are reported in about 5% of breast ultrasound examinations[1]. This work examines the likelihood of malignancy in relation to *sonographically-detected* complex breast cysts.

Methods

We performed a systematic review of the literature on *sonographically-detected* complex breast cysts[1]. We assessed the quality of primary studies using defined criteria[1] and extracted data on cancer detection.

Results

Very few studies have examined complex breast cysts and quantified the associated cancer detection rate, and in most of these studies subjects have been selected on the basis of progress to intervention which would overestimate the likelihood of malignancy. We present our findings in Table 1: the only study to examine complex cysts from all consecutive ultrasounds reported one case of non-invasive cancer from 308 lesions[2] – a low cancer detection rate of 0.3% (95% CI: 0.01 -1.84). Ultrasound features associated with a higher risk of the lesion being a cancer are: thickened walls; thick internal septations; a mix of cystic and solid components; and an imaging classification of indeterminate.

Conclusions

Using the information from our review we categorise complex breast cysts on the basis of associated risk of malignancy[1], and suggest an approach to the management of these lesions to assist clinical decision-making. Provided adequate information is given to the woman, complex breast cysts with a very low risk of malignancy do not always require image-guided biopsy.

References

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Gynaecomastia and male breast cancer – Is cytology sufficient – an EBM approach

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Background

Male Breast cancer represents only 1% breast cancers, though gynaecomastia can affect up to 50% males. Mastectomy prevents approximarely 90% cancers.

Case Report

A 34-year old man presented with recurrent left sided gynaecomastia, first excised at age 29 by subcutaneous mastectomy, and now with "atypical cells" on fine needle aspiration cytology. He subsequently underwent left modified radical mastectomy, which revealed a 32-mm Grade III, node positive (6 out of 20) oestrogen receptor positive tumour. Review of his original pathology prom the excision of his gynaecomastia showed Atypical Ductal Hyperplasia, but no frank cancer.

Gynaecomastia as a premalignant condition

The best evidence regarding gynaecomastia and whether it is premalignant comes from an analysis substantially based on one case control study of 52 cancers with 52 controls, gynaecomastia was found to have a Mantel-Haenszel exposure odds ratio (EOR) of 6.2, (95% confidence limits = 3.4, 11.4), compared with a family history (EOR 2.5) (CL = 1.7, 3.7).

Fine needle aspiration cytology

The best evidence regarding fine needle aspiration cytology in the male breast was a retrospective analysis of 507 aspirates performed on men, 34 of whom had cancer. Of the 15 FNA results which were atypical, 8/15 had benign disease, and 7/15 had cancer.

Recommendation

As gynaecomastia is a common condition, and if fine needle aspiration cytology results are ignored in its treatment, then the number of prophylactic mastectomies needed to be performed to prevent one breast cancer would be approximately 20,000.

If the results of fine needle aspiration cytology are considered, with benign cases observed, and malignant cases removed, then the number of patients with "atypical" fine needle aspiration cytology who will need to undergo mastectomy in order to prevent 90% of breast cancers would be approximately 15/8 i.e. approximately two for each case of breast cancer.

Male ductal carcinoma in-situ: A presentation with blood-stained nipple discharge

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Background

Breast cancer is an uncommon malignancy in males and accounts for less than 1% of newly diagnosed breast cancer overall. Of these, DCIS accounts for approximately 5%.

Methods

We outline a case of pure DCIS in a young man presenting with gynaecomastia and nipple discharge in the setting of anti-psychotic medication for chronic schizophrenia.

Results

A 35 year old man with chronic schizophrenia was referred with a 3 week history of unilateral blood stained nipple discharge occurring spontaneously. He was otherwise asymptomatic and the only family history of note was a paternal cousin diagnosed with breast cancer in her fifties. Examination revealed moderate gynaecomastia without a discrete mass or adenopathy. Ultrasound was unremarkable. A subcutaneous mastectomy revealed a 40mm area of low grade DCIS with an associated intraduct papilloma.

Conclusions

This case supports the literature in that the majority of male DCIS is of low histological grade and of the papillary and cribriform patterns. Following surgical therapy, ongoing follow-up is required due to the risk of local recurrence.

Basal cell carcinoma of the nipple: Another differential diagnosis for Paget's Disease

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Background

Basal cell carcinoma is the most frequently encountered skin malignancy, occurring predominantly on sun-exposed skin. There are approximately 25 reports of its involvement of the nipple-areola complex.

Methods

We present a further case of nipple-areola complex BCC and review the available literature on this rare presentation.

Results

The 75 year old woman presented had noticed nipple ulceration over many years. After imaging, punch biopsies were obtained and found to be consistent with BCC. Wide local excision was performed such that surgical margins were well clear. Histological assessment of the specimen showed infiltration of the nipple and lactiferous ducts to a depth of 6mm.

Conclusions

Although less invasive procedures may be considered in small lesions to optimize cosmesis, this case highlights the need for more aggressive surgery in advanced cases due to the propensity for deeper involvement of epithelial lined lactiferous ducts.

Occult breast cancer presenting as an intramammary node metastasis – Case report and review

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Occult breast cancer presenting as axillary lymph node metastases without an identifiable breast lesion occurs rarely, with reported incidence of 0.3-0.8% of breast cancer presentations. The significance of involvement of these nodes where the primary tumour remains occult is not well described.

Case report

A 67-year-old woman was referred after a screening mammogram showed suspicious microcalcification, in the left upper outer quadrant. Core biopsy of the lesion demonstrated an intra-mammary lymph node containing epithelial cells consistent with metastatic breast carcinoma. Wire localised excision of the lesion demonstrated two small intra-mammary lymph nodes containing suspicious epithelial cells, which stained positive for estrogen receptors. Imaging for a primary tumour including breast MRI and whole body staging investigations failed to demonstrate other abnormalities. The patient was managed expectantly on Tamoxifen 20mg daily with normal breast cancer follow up.

At 63 months post operatively she presented with a three-week history of a small periareolar lump in the ipsilateral breast. After diagnosis by punch biopsy and staging, she proceeded to left mastectomy and axillary dissection. Histology revealed an infiltrating lobular carcinoma with two of fifteen lymph nodes positive. Her endocrine therapy was changed to Letrozole 2.5mg daily and she remains well at 22 months.

Discussion

Occult breast cancers presenting as axillary metastases have been shown to have a rate of subsequent ipsilateral breast “recurrence” if the breast is left in situ and unirradiated to be approximately 57%-69% decreasing to 17%-12.5% with ipsilateral “blind” irradiation. Managed by mastectomy, pathological analysis of the resected breast found malignancy in between 8%. Survival in these series was related to the number of nodes involved. Alternatively, survival may be more akin to the group with positive intramammary nodes with negative axilla at mastectomy with 66% mortality at 10 years for this group.

NOTES

Ultrasound for breast surgeons

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Background and purpose

Ultrasound is becoming more important for surgeons in many disciplines, including breast surgery. This is a report on the early use of ultrasound in a breast surgery practice.

Methods

The results of all ultrasounds performed by a single surgeon over a 2 year period from January 2003 until December 2004 were prospectively collected, including cases where needle biopsy or surgery were performed.

Results

During this period, a total of 153 scans were performed, of which 113 were breast ultrasounds, on 95 women. Just over half of the lesions assessed were impalpable, increasing to three quarters in the second year. A significant number of the ultrasound scans indicated benign breast disease. Needle biopsy was performed in 35 cases (25 fine needle and 10 core), with accurate results for fine needle (2 inadequate samples and 1 false negative). There were 11 cases where impalpable lesions were localised intra operatively and excision confirmed on specimen ultrasound, eliminating the need for pre operative hookwire localisation. Any complex cases or where the lesion was not easily seen were referred to radiologists for further workup.

Conclusions

Breast ultrasound in the office environment is a valuable extension of the examining hands and provides accurate and timely assessment of breast lesions.

Metaplastic carcinoma of the breast – a rare disease: A study of 11 cases

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Background and purpose

Metaplastic breast carcinoma (MBC) is a rare tumour accounting for less than 5% of all breast malignancies. A diagnosis requires the histopathological features of a heterogeneous tumour with mixed cell line origins. Current reports, limited to small case series, indicate that MBC displays a lower incidence of lymph node metastases, a greater propensity to lung metastases and a worse prognosis than other mammary tumours. We describe our comparatively significant experience with MBC in view of the paucity of publications on this rare disease.

Methods

Patients were identified retrospectively using the computer based data system for all breast cancers treated at two affiliated institutions. Clinical information was supplemented from the medical records of each patient.

Results

Eleven patients representing 0.25% of breast cancers recorded in the databases were identified. The median age at presentation was 57 (range 31-77) with a median tumour size of 36 mm (range 6-70 mm). The histopathology was reported as containing predominantly spindle cell metaplastic elements in three patients, more than one metaplastic element in seven patients and no information was available in one case. Three patients were node positive at presentation and two patients were oestrogen and progesterone receptor positive. Lymphovascular invasion was present in one patient. All patients were treated surgically and four patients required re-excision. Combined radiotherapy and cytotoxic or hormone therapy was administered in seven patients. One patient received radiotherapy only. One patient received chemotherapy only, and one patient was treated with tamoxifen only. The overall survival rate was 82%, with average survival duration of 5.4 years (range 0.4 -18.9 years). Three recurrences were observed during a median follow up 5 years, all recurred locally and two metastasized to the lungs. Two patients died from cancer related death, both were node positive and one had vascular invasion.

Conclusions

MBC is a rare subtype of breast cancer. This relatively large series reports that the presence of vascular invasion, lymph node and lung metastases were negative prognostic factors. Contrary to previous reports tumour size was not predictive of survival in this study. Patient age, oestrogen/progesterone receptor status and local recurrence was not found to be predictive of survival. A larger series is required to make more meaningful conclusions.

The Prince of Wales Hospital experience with imprint cytology intra-operative sentinel lymph node assessment

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Introduction

Sentinel lymph node (SLN) Biopsy allows for low morbidity staging of the axilla and avoidance of axillary lymph node dissection for true node negative patients.

Methods available for intra-operative assessment include imprint cytology and frozen section. Advantages of imprint cytology in comparison to frozen section include excellent cytological details and tissue preservation for paraffin section histopathology. We audited our initial experience with imprint cytology for intraoperative assessment of the SLN.

Methods

76 consecutive patients had undergone SLN biopsy and intraoperative evaluation of the SLNs from 8 April 2004 to June 2005 at our unit.

The primary carcinoma pathology included invasive ductal NOS, invasive lobular NOS, mucinous, tubular and cribiform invasive ductal.

The sentinel node was identified through the use of lympho-scintigraphy.

After excision, identified sentinel nodes are delivered fresh to anatomical pathology for imprint cytology assessment.

Sentinel nodes < 6 mm were bisected along longitudinal axis. Those > 6 mm serially sectioned @ approximately 2–3 mm intervals.

Imprint smears made from all cut surfaces (one slide for each cut surface) by touching the surface of the node onto a glass slide.

Slides immediately fixed, stained and then examined by a cytologist.

All slices were then fixed in neutral buffered formalin, processed and embedded into paraffin blocks. Paraffin blocks are each then sectioned @ 6 levels. One section at each level was stained for H&E and a cytokeratin stain (CAM 5.2) was performed on the section @ level 3.

Results

Sensitivity = 57%. Specificity = 100%. Positive Predictive Value = 100%. Negative Predictive Value = 84%. Accuracy = 87%.

Discussion

The intra-operative feedback from imprint cytology at our institution compares well with recent publications. Further analyses of our data will ascertain the sensitivities of imprint cytology for isolated tumour cells and micro-metastases in comparison with macrometastases.