1-3 OCTOBER 2009

SURFERS PARADISE MARRIOTT RESORT & SPA,
GOLD COAST

Australasian Society for Breast Disease

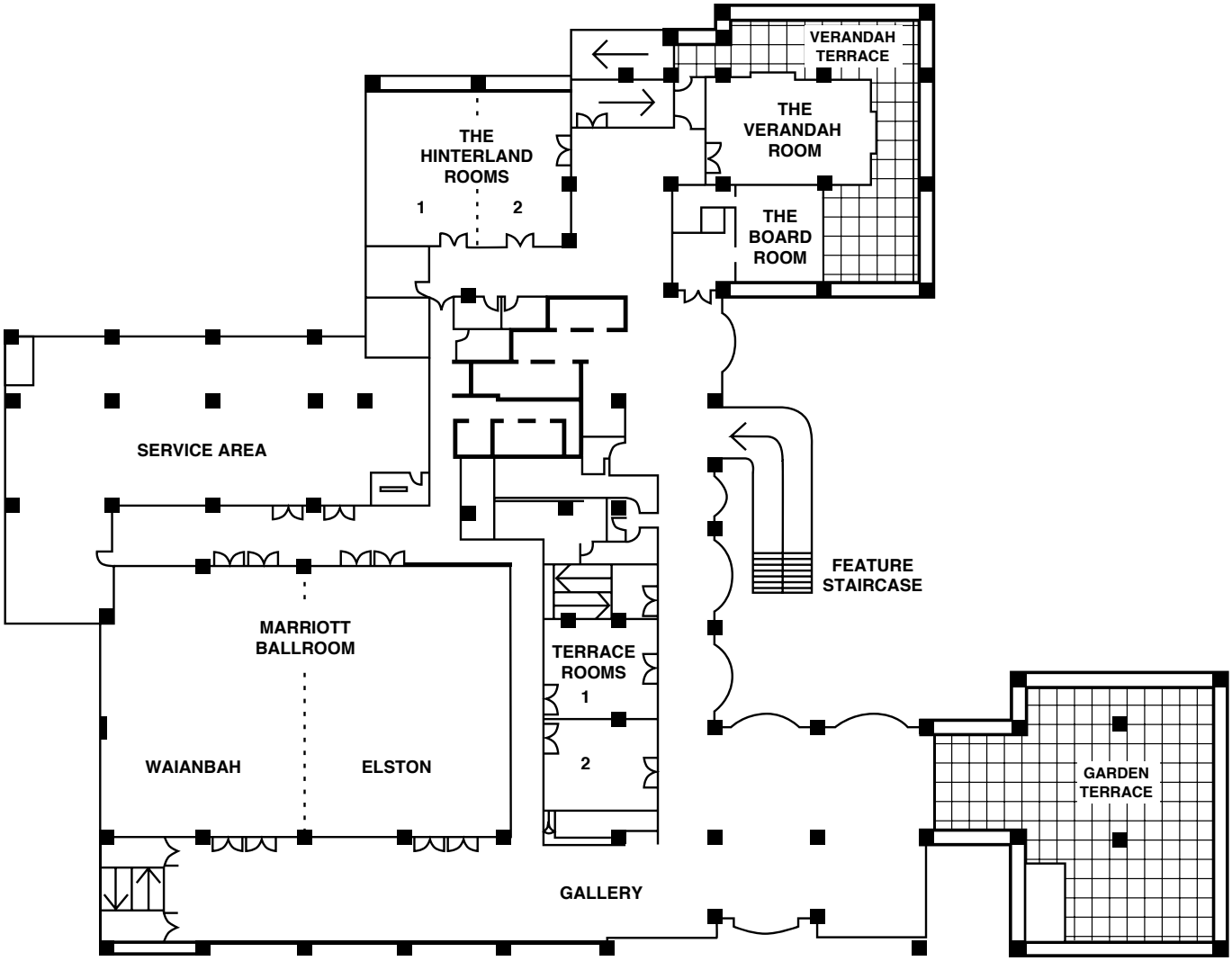
Dedicated to promoting knowledge in the areas of prevention, diagnosis & management of breast disease

Seventh Scientific Meeting

HANDBOOK AND ABSTRACTS

SURFERS PARADISE MARRIOTT RESORT & SPA, GOLD COAST

Conference Level



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Section I
Handbook

Welcome

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

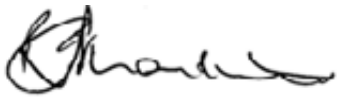
This Meeting is designed to advance your knowledge in the areas of the latest techniques of investigation and management of breast disease. As our core educational activity the Meeting will again have a strong multidisciplinary emphasis. In addition, the Scientific Meeting provides an important forum for professional and social interaction between delegates from the various disciplines.

I wish to thank our sponsors AstraZeneca Oncology, Novartis Oncology, Roche Products, Sanofi-Aventis, GE Healthcare, SonoSite and Mentor as well as all the exhibitors for their tremendous support. It would not be possible to hold this Scientific Meeting without their support. Please take the time to meet with the representatives of the participating companies.

If you are not a member of ASBD, we would like you to consider joining. Membership application forms are available from the Meeting Office.

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.

I trust that this will be a great Meeting and that you will enjoy all aspects of it.



Robin Stuart-Harris

President

Executive Committee

Prof Robin Stuart-Harris	Medical Oncologist, President
Dr Marie-Frances Burke	Radiation Oncologist, Secretary/Treasurer
Dr Natacha Borecky	Radiologist
Dr Roslyn Drummond	Radiation Oncologist (co-opted)
Dr Susan Fraser	Breast Physician (co-opted)
Prof Michael Friedlander	Medical Oncologist (co-opted)
A/Prof Bruno Giuffre	Radiologist (co-opted)
Prof Jennet Harvey	Pathologist (co-opted)
A/Prof Nehmat Houssami	Breast Physician / Clinical Epidemiologist
Dr James Kollias	Surgeon
Dr Warwick Lee	Radiologist
Dr Julia Leeds	BCNA Representative (co-opted)
Dr Lynne Mann	Surgeon
Dr Kerry McMahon	Radiologist (co-opted)
Dr Wendy Raymond	Pathologist
Dr Belinda Scott	Surgeon (co-opted)
Dr Daniel de Viana	Surgeon
Ms Solei Gibbs	Executive Officer

Previous Executive Committee Members

Dr Geoffrey Beadle	Medical Oncologist
A/Prof Michael Bilous	Pathologist
A/Prof John Boyages	Radiation Oncologist
Dr Colin Furnival	Surgeon
Prof Michael Green	Medical Oncologist
Dr Cherrell Hirst	Breast Physician
Ms Elspeth Humphries	BCNA Representative (co-opted)
Dr Michael Izard	Radiation Oncologist
Dr Jack Jellins	Scientist
Ms Veronica Macaulay-Cross	BCNA Representative (co-opted)
Mr William McLeay	Surgeon
Ms Lyn Moore	BCNA Representative (co-opted)
Dr Margaret Pooley	Surgeon
A/Prof Mary Rickard	Radiologist

About the Australasian Society for Breast Disease

The Australasian Society for Breast Disease was constituted in 1997. Its primary goal is to promote multidisciplinary understanding and practice in the prevention, detection, diagnosis and management of breast disease and research into this area of medicine.

The Society has a nine-member Executive plus several co-opted members, providing for broad multidisciplinary representation.

The Society thanks current members for their support and involvement and welcomes new members from all disciplines involved in the area of breast disease. You can download a membership application form from our website: www.asbd.org.au or contact the Secretariat.

Contact Details

Australasian Society for Breast Disease
PO Box 1124
Coorparoo DC Qld 4151
Tel: (07) 3847 1946 (from overseas: +61 7 3847 1946)
Fax: (07) 3847 7563 (from overseas: +61 7 3847 7563)
Email: info@asbd.org.au
Website: www.asbd.org.au

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As one of the world's leading pharmaceutical companies, AstraZeneca is engaged in the research, development, manufacture, and supply of medicines that make a difference for patients in important areas of healthcare.

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Locally, AstraZeneca has spent over $250 million over the last decade on R&D, and is currently involved in over 50 clinical trials at over 200 sites across Australia.

AstraZeneca's Sydney manufacturing facility is a key part of the global manufacturing network, employing more than 500 people and providing niche products to 37 international markets.

Globally, the Company spends more than $16 million every working day on R&D, with more than 13,000 researchers dedicated to the discovery and development of innovative new medicines that meet the needs of patients worldwide.

AstraZeneca believes that it has a global responsibility to its customers and the communities they live in.

Through financial support and representation, AstraZeneca recognises the work and commitment of patient care and advocacy groups. These important partnerships are central to our commitment to improve the quality of people's lives.

AstraZeneca Australia also has a proud history of supporting the local community. Since 2005, AstraZeneca's support has assisted Redkite in providing children and their families battling with childhood cancer, with fundamental services, both financial and emotional.

Every day, more than 1.5 million Australians benefit from AstraZeneca medicines.

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NOVARTIS

ONCOLOGY

Novartis Oncology provides a range of innovative therapies and practical solutions that aim to improve and extend the lives of cancer patients. We aspire to develop new medicines that will transform the way cancer is treated, and are therefore committed to ongoing research and development in Australia and New Zealand. Our current portfolio includes:

Glivec (imatinib) for the treatment of CML and GIST as well as in a subset of patients with Ph+ALL, HES/CEL, MDS/MPD, DFSP, ASM;

Tasigna (nilotinib), for the treatment of adults with chronic or accelerated phase (CML) resistant to or intolerant of prior therapy including imatinib;

Femara (letrozole), for the treatment of postmenopausal women with hormone receptor positive breast cancer;

Zometa (zoledronic acid), for prevention of skeletal-related events in multiple myeloma and advanced malignancies involving bone, including breast, prostate and lung cancers, as well as the treatment of hypercalcaemia of malignancy;

Sandostatin LAR (long acting octreotide), for the symptomatic control and reduction of GH and IGF-1 in patients with acromegaly and to control symptoms in patients with functional carcinoid tumours and VIPomas; and

Exjade (deferasirox), for the treatment of chronic iron overload due to blood transfusions (transfusional haemosiderosis).

Unrestricted Education Grants – Medical Oncology Trainees

Roche

Roche is the world's leading provider of cancer care products, including anti-cancer treatments and diagnostics. As the world's biggest biotech company and an innovator of products and services for the early detection, prevention, diagnosis and treatment of diseases, Roche contributes on a broad range of fronts to improving people's health and quality of life.

Bronze Sponsor

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MENTOR
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Trade Exhibition

Booth no.	Company
1. & 2.	GE Healthcare
3.	ImpediMed
4.	Schering-Plough
5.	Queensland X-Ray
6.	National Breast Cancer Centre
7. & 8.	Roche Products
9.	Hologic
10. & 11.	Novartis Oncology
12. & 13.	SonoSite
14. & 15.	AstraZeneca Oncology
16.	AstraTech
17. & 18.	Sanofi-Aventis
19.	Bard Australia

Useful Information

Venue

Surfers Paradise Marriott Resort & Spa
158 Ferny Avenue
Surfers Paradise Qld 4217
Australia
Tel: (07) 5592 9800 (from overseas: +61 7 5592 9800)
Fax: (07) 5592 9888 (from overseas: +61 7 5592 9888)

Meeting Office

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

Thursday 1 October 2009	0730-1900 hours
Friday 2 October 2009	0730-1730 hours
Saturday 3 October 2009	0730-1500 hours

Speakers' Audiovisual Testing Room

The Speakers' Audiovisual Testing will be available in Terrace Room II on level 2 during the following times:

Thursday 1 October 2009	1500-1800 hours
Friday 2 October 2009	0730-1600 hours
Saturday 3 October 2009	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.

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 & Spa (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. A jacket may be needed for air conditioned Meeting rooms. Dress for Meeting dinner is cocktail wear / Shanghai theme.

Social Program

Lunches

Lunches will be served in the Garden Terrace and the Trade Exhibition area. Lunch service is by ticket only. Please ensure you have the correct tickets. Additional tickets are available at $40 per person.

Welcome Drinks

Thursday 1 October 2009, 1830-1930 hours

Meet your fellow delegates for a relaxed drink by the pool area or, in case of the weather not being favourable, in the Garden Terrace. Included for fulltime delegates and registered partners. Additional tickets cost $40 per person.

Networking Drinks

Friday 2 October 2009, 1730-1900 hours

Following the last session for the day, catch up with your colleagues at drinks in the Trade Exhibition area. Included for fulltime and Friday delegates and registered partners only. No additional tickets.

Meeting Dinner

Sponsored by Novartis Oncology

Saturday 3 October 2009, 1930-2300 hours

Join your fellow delegates and be transported to the romance of old colonial Shanghai. To conclude the Meeting, the Marriott Ballroom will be transformed into the famous Shanghai Club. Open your senses to experience the fine flavours of EuroAsian blend and relax to the sounds of Ingrid James & East Coast Ensemble. The dinner will include pre dinner refreshments in the Garden Terrace, dinner and drinks. Included for fulltime delegates and registered partners. Additional tickets: $120 per person. Cocktail wear / Shanghai theme.

Annual General Meeting

The Annual General Meeting of the Australasian Society for Breast Disease will be held in the Verandah Room at 0730 hours on Saturday 3 October 2009. Breakfast will be served during the Meeting. Please reconfirm you attendance / nonattendance upon registration. Admission is free to members only.

Optional Social Activities

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

Breast Physicians

The Australasian Society of Breast Physicians will host a supper for its members at 1900 hrs on Friday 2 October 2009, in the Boardroom.

Consumer Forum

Australasian Society for Breast Disease and Breast Cancer Network Australia will host a joint Forum for Consumers - *Living Well after Breast Cancer* - on Saturday 3 October 2009, from 0900 hours in the Hinterland Rooms. Speakers will include Dr Sandi Hayes, Tara Diversi, Raelene Boyle and Dr Jane Turner.

CPD

RACS

This educational activity has been approved in the Royal Australasian College of Surgeons' Continuing Professional Development (CPD) Program. Fellows who participate can claim one point per hour (maximum 22 points) in Category 4: Maintenance of Clinical Knowledge and Skills towards 2009 CPD totals.

RANZCR

The Royal Australian and New Zealand College of Radiologists will award points as follows:

- 13.5 points may be claimed for attendance at one workshop and the symposium on Thursday 1 October 2009.
- 6.5 points may be claimed for attendance at the Meeting on Friday 2 October 2009.
- 6 points may be claimed for attendance at the Meeting on Saturday 3 October 2009.
- For anyone attending only part of this Meeting, points may be claimed pro rata at 3 points per learning hour for workshops and 1 point per hour for lectures.

RACGP

Breast Physicians and General Practitioners can access the RACGP website www.racgp.org.au to determine the QA points on an individual basis (Category 2) for Meeting attendance.

Keynote speakers

Prof Fiona J Gilbert MBChB, DMRD, FRCP, FRCR

Fiona Gilbert qualified in medicine from the University of Glasgow in 1978. She was appointed consultant radiologist in 1989 in Aberdeen, running the breast screening programme and symptomatic breast services. In 1996, she was appointed Roland Sutton Chair of Radiology, University of Aberdeen and Head of Department. Professor Gilbert's research is focussed on breast, oncology and musculo-skeletal imaging. She heads the MRI research programme and is leader of the University Imaging programme. She is vice-chair of the Royal College of Radiologists Breast Group, member of the NCRN breast focus group and co-lead of the NCRI PET research development group. Professor Gilbert referees for Radiology and the Breast and referees grant applications for Chief Scientist's Office, Cancer Research UK and other funding bodies. She is a member of the MRC panel of experts and Academic Role model for the British Medical Association. She has grants from the HTA, MRC, CRUK and CSO.

Prof Daniel F Hayes MD

Daniel Hayes is the Clinical Director of the Breast Oncology Program at the University of Michigan Comprehensive Cancer Center (UM CCC), where he is also Professor of Internal Medicine. He received his MD from the Indiana University School of Medicine in 1979. Professor Hayes served a fellowship in medical oncology from 1982–1985 at Harvard's Dana Farber Cancer Institute, in Boston. In 1992, he assumed the role of Medical Director of the Breast Evaluation Center at DFCI. In 1996 he moved to the Georgetown University Lombardi Cancer Center. In 2001, Professor Hayes joined the UM CCC where he continues clinical work and research in translational science. With his long-time colleague, Donald Kufe, Professor Hayes published the first reports concerning the development of the CA15-3 blood test, now used worldwide to evaluate patients with breast cancer. He is an internationally recognized leader in the use of this and other tumour markers. In 2007, he was awarded the American Society of Clinical Oncology's (ASCO) Gianni Bonadonna Breast Cancer Award. Professor Hayes is Chair of the Breast Cancer Translational Medicine Committee of the Southwest Oncology Group (SWOG), Chair of the Correlative Sciences Committee of the U.S. Breast Cancer Intergroup, and co-chairs the Expert Panel for Tumor Marker Practice Guidelines for the American Society of Clinical Oncology (ASCO).

Prof Kelly K Hunt MD, FACS

Kelly Hunt is Professor of Surgery and Chief of the Surgical Breast Section at The University of Texas MD Anderson Cancer Center in Houston, Texas. She is Chair of the Breast Organ Site Committee of the American College of Surgeons Oncology Group. Professor Hunt received her medical degree with highest honours from The University of Tennessee and completed postgraduate training at the University of California Los Angeles. She completed a surgical oncology fellowship at MD Anderson Cancer Center and remained on faculty following her training. Professor Hunt has published over 280 peer-reviewed articles and has edited three books on breast cancer and one on gene therapy. She is the Principal Investigator on 12 clinical research trials, and directs a research laboratory. Her primary research interests are cell cycle deregulation, gene therapy and tumour suppressor genes, and clinical interests include breast conservation, sentinel lymph node biopsy, and skin-sparing mastectomy.

Prof Jean F Simpson MD

Jean Simpson was born and raised in Columbus, Georgia, where she also received her undergraduate degree from Columbus College. Early in her second year of medical school at The Medical College of Georgia (MCG) in Augusta, she decided that Pathology would be her career choice. Upon graduating from MCG, she undertook residency training in Anatomic and Clinical Pathology at Vanderbilt University Medical Center in Nashville, Tennessee. Professor Simpson then completed a Medical Staff Fellowship at the National Cancer Institute, National Institutes of Health in Bethesda, Maryland, where she worked in the field of tumour immunology. She returned to Vanderbilt for Surgical Pathology Fellowship under the direction of David Page, and then joined the Pathology Faculty as Assistant Professor. She spent six years at the City of Hope Medical Center in Duarte, California, and returned to Vanderbilt in 1997, where she currently is Professor of Pathology. Her professional interests include diagnostic histopathology and molecular analysis of premalignant breast disease.

Faculty Members

Dr Melissa Bochner MBBS, FRACS, MS

Melissa Bochner trained in breast surgery at the Royal Adelaide Hospital in 1998 and Edinburgh Breast Unit in 1999. Her current positions are Staff Specialist Surgeon, Royal Adelaide Hospital Breast Endocrine and Surgical Oncology Unit, and Visiting Medical Specialist, BreastScreen SA. She is a member of the expert advisory panel for National Breast and Ovarian Cancer Centre (NBOCC) and has worked with the NBOCC on guideline development in several areas. Dr Bochner is a member of the Breast and Endocrine sections of the Royal Australasian College of Surgeons and is the Royal Adelaide Hospital Supervisor of Pre-SET trainees.

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 Premion, Brisbane. Dr Burke's major interests are in breast and gynaecologic cancers. She is the current Secretary / Treasurer for the Australasian Society of Breast Disease.

A/Prof Jennifer Cawson MBBS, MPH, MD, FRANZCR

Jenny Cawson is a graduate of Melbourne University and has wide experience in breast imaging, screening for breast cancer, and breast cancer research. She is Director of St Vincent's BreastScreen, an Associate Professor at the University of Melbourne and is/was on committees of RANZCR, BreastScreen Australia, BreastScreen Victoria and other national and state bodies. She is the founder and convener of the Breast Imaging Group of the RANZCR. Among other research interests, she is involved in investigating breast density and its effect on breast cancer risk and the links between breast density and breast cancer genetic factors. She has a strong interest in education and speaks at local, national and international conferences. Professor Cawson offers training in breast imaging including Fellows positions to Australian and ASEAN radiologists.

Dr David Clark BSc, MBBS, FRACS

David Clark is a Surgeon and is the Director of The Breast Centre in Newcastle, a multidisciplinary clinic caring for 350 new patients with breast cancer each year. There are on-site radiological and cytological services, enabling diagnosis of most breast problems within minutes. The Centre was established in 1987 and comprises surgeons, radiologists, pathologists, medical and radiation oncologists, a psycho-oncologist and nurse counsellor and a physiotherapist. There is also a fulltime research co-ordinator.

Ms Sue Davies DMU, AMS

Sue Davies is the Program Director and co-founder of the Australian Institute of Ultrasound; the foremost practical ultrasound education facility in the Asia-Pacific region and she is an Honorary Fellow of ASUM. A highly experienced and passionate teacher, Ms Davies has been involved in ultrasound education both in Australia and internationally for over 35 years and she has been teaching point of care ultrasound to physicians of many specialties for more than 15 years.

Dr James French MBBS (Hons) FRACS

James French is the Head of Breast Surgery at the NSW Breast Cancer Institute, located at Westmead Hospital. He holds various VMO appointments, and is Chairman of the Department of Surgery at The Hills Private Hospital. Dr French completed a Fellowship in Breast and Endocrine Surgery at the Queen Alexandra Hospital in Portsmouth UK. He is involved in numerous clinical research projects including SNAC 2, IBSCG 23 Micro-Metastasis Trial, and will be involved in an upcoming multicentre Lymphoedema Assessment Trial. Dr French has a keen interest in the application of new technologies to clinical practice, and is committed to teaching general surgical trainees.

Prof Jennet Harvey MBBS, FRCPA

Jennet Harvey is Winthrop Professor at The University of Western Australia. 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 a Councillor, Australian Council on Smoking and Health and a past President of the Australasian Society for Breast Disease.

A/Prof Nehmat Houssami
MBBS (Hons), MPH, M Ed, FAFPHM, FASBP, PhD

Nehmat Houssami is a Breast Physician and a Clinical Epidemiologist and has worked in breast services for the past 20 years. She has experience in clinical and epidemiological research in various aspects of breast diagnostics including imaging, screening, staging and prognostic testing. Professor Houssami works as a Breast Physician at the Royal Hospital for Women (Sydney), and is Principal Research Fellow with the Screening & Test Evaluation Program, School of Public Health, Sydney Medical School (University of Sydney) where she currently leads the breast cancer research portfolio. She is a research affiliate with the NSW Breast Cancer Institute and with the Istituto per lo Studio e la Prevenzione Oncologica (ISPO, Florence). She has 90 publications in the peer-reviewed literature, and is Specialty Editor for 'Imaging, Screening & Early Diagnosis' with *The Breast*.

Dr Lizbeth Kenny MBBS, FRANZCR

Liz Kenny graduated in Medicine from The University of Queensland in 1980, and completed her specialty training in radiation oncology at The Queensland Radium Institute in Brisbane in 1987. She is a Senior Radiation Oncologist at The Royal Brisbane and Women's Hospital. Her main areas of specialty interest are Head and Neck Cancer and Breast Cancer. In 2005 Dr Kenny was appointed as Medical Director, Cancer Services Central and is committed to improving Cancer Services in Queensland. She currently also serves as the Clinical Lead for the Queensland Health Imaging Program. She has served as The Dean of The Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists and the President of The Clinical Oncological Society of Australia. She is the immediate past President of The Royal Australian and New Zealand College of Radiologists. During 2008 Dr Kenny was awarded an Honorary Membership of The European Society of Radiology and an Honorary Fellowship of The American College of Radiology. During 2009 she will be awarded an Honorary Membership of the Radiological Society of North America.

Dr 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 the current Chairman of the Royal Australian College of Surgeons (RACS) Breast Section and the Clinical Director of the RACS National Breast Cancer Audit. Dr Kollias' special interests include breast training and oncoplastic breast surgery. He has published over 50 scientific manuscripts in scientific refereed journals and book chapters.

Prof Sunil R Lakhani MD, FRCPath (UK), FRCPA

Sunil Lakhani is Professor and Head of Molecular & Cellular Pathology in The School of Medicine, University of Queensland. He is Head of the Breast Group at the University of Queensland Centre for Clinical Research (UQCCR) and Visiting Breast Pathologist at The Royal Brisbane and Women's Hospital. He is lead pathologist for North Brisbane Breast Screening Service. Prior to his move to Australia in 2004, he was Professor of Pathology at The Institute of Cancer Research and the Royal Marsden Hospital, London, UK. He has authored/edited a number of undergraduate and postgraduate textbooks and book chapters and published more than 150 scientific papers. He is a series editor for the WHO Tumour Classification Books and on the panel for the WHO Classification of Tumours of the Breast. Professor Lakhani is deputy editor of *Breast Cancer Research* and on the board of *Journal of Pathology, Virchow's Archives* and *International Journal of Experimental Pathology.* He sits on a number of national and international advisory panels and working groups including National Pathology Accreditation Advisory Council – Cancer Genetics Panel, Kathleen Cunningham Foundation for Research into Familial Breast and Ovarian cancer (KConFab) and The International Cancer Genome Consortium (ICGC) for Breast Cancer.

Dr Wendy Raymond MBBS, MD, FRCPA

Wendy Raymond is a Pathologist with a longstanding interest in breast disease having completed an MD on "Immunohistochemical markers in Breast Carcinoma" in 1991. She is a consultant pathologist at Flinders Medical Centre, a Visiting Specialist Cytopathologist at BreastScreen SA and a part-time consultant in private practice at Gribbles Pathology. Dr Raymond is a co-author of the ACN sponsored "*The pathology reporting of Breast Cancer Guidelines*", is a member of the Australasian Society for Breast Disease Executive, has served on Quality Assurance Committees of the RCPA in breast pathology and cytopathology and is an examiner for the Royal College of Pathologists.

Prof Nigel Sacks MD, FRACS, FRCS (Eng Hon)

Nigel Sacks is the University of Adelaide Professor of Breast and Endocrine Surgery at the Lyell McEwin Hospital in Adelaide. He originally trained in Breast, Endocrine and Plastic surgery at the Royal Melbourne Hospital and he then undertook post-fellowship training in Breast Reconstructive and Oncoplastic surgery in Nottingham and Oxford in the UK and Memorial Sloane Kettering Hospital in New York. Professor Sacks took up a Consultant post at The Royal Marsden Hospital in 1990 at the age of 33. He worked there for 19 years publishing more than 100 peer reviewed papers in medical journals, pioneering immediate breast reconstruction there with a personal series of more than 750 cases and he performed the first sentinel node biopsy in the UK in 1997. His research interests include the endocrine therapy of breast cancer, breast cancer genetics, breast tumour biomarkers and breast screening.

Dr Catherine Shannon MBBS (Hons) FRACP

Catherine Shannon is a Consultant Medical Oncologist at the Mater Adult Hospital Brisbane and a member of the MMRI's Clinical Research group. She is the principal or co-investigator on a number of phase I, II and III clinical trials in breast, gynaecological and lung cancer. She is currently on the Executive Committee of the Medical Oncology Group of Australia and the medical oncology consultant for the National Breast and Ovarian Cancer Centre. More recently she chaired the committee in writing endocrine therapy guidelines for the management of advanced breast cancer. Dr Shannon has previously completed a fellowship with the Breast Cancer Unit of the Royal Marsden Hospital. Here her research centered on the pre-operative endocrine therapy of breast cancer and the use of biological markers as predictors of response to treatment. She obtained extensive experience in phase I and II trials of novel agents for metastatic breast cancer. Her research publications include work on the molecular genetics of synchronous gynaecological tumours and neoadjuvant therapies for breast cancer. Dr Shannon has a special interest in the management of breast cancer in young women and pregnant women and has published in this field.

Prof Robin Stuart-Harris MD, FRCP, FRACP

Robin Stuart-Harris trained in medical oncology and palliative care at the Royal Marsden Hospital, London, United Kingdom, 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. He remains a Senior Staff Specialist in Medical Oncology, but is also Clinical Director of the Capital Region Cancer Service. He has particular interests in the management of both early and advanced breast cancer and the psychosocial aspects of cancer. Professor Stuart-Harris is the current President of the Australasian Society for Breast Disease.

Dr Daniel de Viana MBBS, RACS

Daniel de Viana is a medical graduate from the Queensland University, who completed his general surgery training through Princess Alexandra Hospital, Brisbane. He undertook postgraduate training in breast surgery and cancer management in the United Kingdom. He settled on the Gold Coast in 1999, initially working as Staff Breast Surgeon at the Gold Coast Hospital, and commenced private practice in 2000. Dr de Viana is a consultant at BreastScreen Southport, member of surgical review panel of BreastScreen Queensland, member of Executive Committee of the Australasian Society for Breast Disease, member of Royal Australasian College of Surgeons Breast Section, and member of the International Society of Breast Disease.

Dr Duncan Walker MRCP (UK), FRCR, FRANCR

Duncan Walker is an Interventional Radiologist. Since joining the staff at the Wesley Hospital, he has worked in both diagnostic radiology and in interventional radiology (IR) where the service has developed into a comprehensive program staffed by two dedicated radiologists each day. To cover leave and other commitments, there are now five radiologists staffing the IR service and there is internal cover on weekday nights and a shared on call roster at weekends that covers the Wesley, Royal Brisbane and Princess Alexandra sites for procedural sites. A broad range of interventional radiology services are offered, including physical treatments for cancer such as radiofrequency ablation, chemoembolisation and Yttrium microspheres. Dr Walker has been a member of the Wesley Research Institute since its inception and has published articles on tendon injury and adaptive responses to exercise using MRI data to measure muscle volumes.

Dr Nicholas Wilcken PhD, FRACP

Nicholas Wilcken is Director of Medical Oncology at Westmead and senior staff specialist at Nepean Hospital, and Senior Lecturer, University of Sydney. He did his oncology training at Royal Prince Alfred Hospital, Sydney, followed by a PhD at the Garvan Institute in Sydney, studying the cell cycle regulation of breast cancer cells. He has also been involved in clinical epidemiology projects (mainly systematic reviews) and guideline development for the National Breast Cancer Centre of Australia. He is currently co-ordinating editor for the Cochrane Collaboration Breast Cancer Group, Director of Research at the NSW Breast Cancer Institute and Deputy Chair of the ANZ Breast Cancer Trials Group's Scientific Advisory Committee.

Presenters - Proffered Papers

Dr Rosemary Balleine MBBS (Hons), PhD, FRCPA

Staff Specialist and Cancer Institute NSW Fellow, Sydney West Area Health Service, Westmead Millennium Institute and University of Sydney, Australia

Dr Meagan Brennan BMed, DFM, FRACGP, FASBP

Clinical Senior Lecturer, University of Sydney and Staff Specialist Breast Physician, Royal North Shore and Westmead Hospitals, Sydney, NSW, Australia

Dr Yew Choy Cheong MBBS

Resident Medical Officer, The Queen Elizabeth Hospital, Adelaide, SA, Australia

A/Prof Laval Grimard MD, FRCPC

Head, Division of Radiation Oncology, Department of Radiology, The Ottawa Hospital Cancer Centre, Ontario, Canada

Dr Ewan KA Millar FRCPath, FRCPA

Staff Specialist, SEALS Anatomical Pathology, St George Hospital & Cancer Research Program, Garvan Institute of Medical Research, Sydney, and Cancer Institute NSW Clinical Research Fellow, Australia

Dr Nirmala Pathmanathan BSc (Med), MBBS, FRCPA, MIAC

Staff Specialist, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Breast Pathologist, Breast Cancer Institute and BreastScreen Greater Western Sydney, and Research Fellow, Westmead Millennium, Sydney, NSW, Australia

Venues

Thursday 1 October 2009

0730-1900 hrs	Registration Venue: Terrace Room I
1500-1800	Speakers' audiovisual testing Venue: Terrace Room II
0800-1200	Workshop: Introduction to Ultrasound for Clinicians Venue: Hinterland Rooms
1230-1630	Workshop: Advanced Ultrasound Techniques for Clinicians Venue: Hinterland Rooms
1830-1930	Welcome drinks Venue: Pool side

Friday 2 October 2009

0730-1730	Registration Venue: Terrace Room I
0730-1600	Speakers' audiovisual testing Venue: Terrace Room II
1730-1900	Networking drinks Trade Exhibition area
1900-2030	Australasian Society for Breast Physicians supper Venue: Boardroom

Saturday 3 October 2009

0730-1500	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
0900-1230	Consumer forum Hinterland Rooms
1930-2300	Meeting dinner Venue: Garden Terrace / Ballroom

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

Program

Please note that the program is subject to change.

Thursday 1 October 2009

0730-1900 hrs	Registration	
0800-1200	**Workshop 1: An Introduction to Ultrasound for Clinicians** *Sponsored by GE Healthcare and SonoSite*	
1230-1630	**Workshop 2: Advanced Ultrasound Techniques for Clinicians** *Sponsored by GE Healthcare and SonoSite*	
1700-1830	**Minisymposium: Should women with newly diagnosed breast cancer have MRI staging of the affected breast?** *Sponsored by AstraZeneca Oncology*	
	Co-chairs: Nehmat Houssami and Robin Stuart-Harris	
	An imaging perspective	**Fiona Gilbert**
	A surgical perspective	**James French**
	Pre-operative MRI to "stage" patients with histologically documented primary breast cancer	**Daniel Hayes**
	A radiation oncology perspective	**Liz Kenny**
	Discussion	**Faculty and Kelly Hunt**
1830-1930	Welcome drinks	

Friday 2 October 2009

0900-1030	**Session 1: Breast Cancer in Elderly Women** *Sponsored by AstraZeneca Oncology*	
	Chair: Robin Stuart-Harris	
	Welcome	**Robin Stuart-Harris**
	Breast carcinoma in the elderly: Is it different?	**Jean Simpson**
	Should elderly women have full surgery?	**Nigel Sacks**
	Tailoring radiotherapy for elderly women	**Marie Burke**
	Is chemotherapy contraindicated in elderly women?	**Daniel Hayes**
	Discussion	**Faculty**
1030-1100	Morning break	
1100-1245	**Session 2: Emerging Trends in Early Breast Cancer**	
	Chair: Daniel de Viana	
	Is there a role for computer-aided detection in screening?	**Fiona Gilbert**
	Keynote address: The "continuum" from benign to malignant breast disease	**Jean Simpson**
	Cryoablation therapy in benign and malignant disease	**Kelly Hunt**
	Decision making in immediate breast reconstruction	**Melissa Bochner**
	Discussion	**Faculty**
1245-1345	**Lunch**	

1345-1500	**Session 3: Proffered Papers**	
	Chair: Wendy Raymond	
	Prediction of local recurrence, distant metastases and death following breast-conserving therapy in early-stage invasive breast cancer using a five biomarker panel	**Ewan Millar**
	Meta-analysis of preoperative contralateral MRI in women newly diagnosed with invasive breast cancer	**Meagan Brennan**
	Interval between breast-conserving surgery and radiotherapy in early-breast cancer: How long before an effect on local control?	**Laval Grimard**
	Mastectomy and reconstruction: An increasing trend in the last 10 years	**Yew Choy Cheong**
	Core biopsy evaluation of papillary lesions of the breast	**Nirmala Pathmanathan**
	The breast cancer tissue bank	**Rosemary Balleine**
1500-1530	Afternoon break	
1530-1730	**Session 4: Prevention, Detection and Prognostication**	
	Chair: Nehmat Houssami	
	Keynote address: Are circulating cells an established prognostic factor?	**Daniel Hayes**
	The role of genomics in predicting prognosis	**Sunil Lakhani**
	Keynote address: Screening for high risk women	**Fiona Gilbert**
	Keynote address: The use of prophylactic surgery in high risk women	**Kelly Hunt**
	Discussion	**Faculty**
1730-1900	Networking drinks	

Saturday 3 October 2009

0730-0900	Registration	
0730-0845	ASBD Annual General Meeting	
0900-1030	**Session 5: The Management of Metastatic Disease** *Sponsored by Roche Products*	
	Chair: Robin Stuart-Harris	
	Pathological predictors of locoregional and distant metastasis: Part 1	**Jean Simpson**
	Is metastatic breast cancer curable?	**Nicholas Wilcken**
	Breast surgery in the context of metastatic disease	**Kelly Hunt**
	Targeted treatments for metastatic disease	**Daniel Hayes**
	Discussion	**Faculty**
1030-1100	Morning break *Sponsored by Sanofi-Aventis*	
1100-1230	**Session 6: Isolated Metastatic Disease**	
	Chair: Marie-Frances Burke	
	Interventional radiology therapy for breast cancer metastatic to liver	**Duncan Walker**
	Pathological predictors of locoregional and distant metastasis: Part 2	**Jean Simpson**
	Case presentations	**Faculty and Robin Stuart-Harris, Roslyn Drummond and Daniel de Viana**
1230-1330	Lunch	

1330- 1515	**Session 7: Improving Quality of Care** *Sponsored by AstraZeneca Oncology*	
	Chair: Jennet Harvey	
	Current status of tumour receptor analysis	**Wendy Raymond**
	Challenges in population screening in Australia	**Jennifer Cawson**
	MRI features of cancers in high risk women and *BRCA1* and *BRCA2* carriers	**Fiona Gilbert**
	Using evidence to select systemic therapy	**Daniel Hayes**
	Optimal adjuvant endocrine therapy for early breast cancer	**Robin Stuart-Harris**
	Discussion	**Faculty**
1515-1545	Afternoon break	
1545-1700	**Session 8: LABC and Neoadjuvant Treatment** *Sponsored by Novartis Oncology*	
	Chair: James Kollias	
	The MD Anderson approach to neoadjuvant therapy	**Kelly Hunt**
	Monitoring neo-adjuvant chemotherapy	**Fiona Gilbert**
	Neoadjuvant endocrine therapy or chemotherapy?	**Catherine Shannon**
	Discussion	**Faculty**
	Awards for best proffered paper and best poster	
	Closing comments	**Robin Stuart-Harris**
1930-	Dinner *Sponsored by Novartis Oncology*	

Section II
Abstracts

Notes

WORKSHOP: ADVANCED ULTRASOUND TECHNIQUES FOR CLINICIANS

Sponsored by GE Healthcare and SonoSite

Notes

Intraoperative ultrasound

David Clark
The Breast Centre, Newcastle, NSW, Australia

Preoperative hookwire localizations are commonly used to guide the excision of subclinical breast lesions. With the availability of ultrasonography in the operating theatre, the vast majority of these localizations can be performed intraoperatively. Preoperative hookwire localizations are not without problems and complications. The risk of missing the relevant lesion varies from 0 to 22 %. They are also time-consuming, require coordination of the patient, radiologist and radiographer and may be quite distressing for some patients, especially if the localizations are difficult. There are also the possibilities of wire displacement and unnecessarily large volumes of breast tissue excision. From June 2003 we have performed more than a thousand of these procedures intraoperatively and find the procedure simple, reliable, rapid and cost-effective. It is particularly useful in ensuring adequate but not excessive margins in breast conserving surgery for cancers.

Ideally, the location of the lesion is verified preoperatively. In the operating theatre, the ultrasound probe and lead are covered in a sterile plastic sheath. The patient is prepped and draped and sterile gel is placed inside the plastic sheath and on the skin over the predicted location of the lesion. The lesion is found and a long 23-G needle is passed into it, as would be done when performing fine-needle aspiration cytology. The location of the lesion is marked on the skin and a cosmetically appropriate incision is made. Dissection continues until the needle is located proximal to the lesion and the lesion is excised (if benign or for biopsy purposes) or widely excised (if malignant). The specimen is orientated with sutures and immediately checked with specimen ultrasonography. If a wide excision has been performed, margins around the cancer are measured.

The important steps for using this method are:

1. Ensure that the resolution of the ultrasound machine used in the operating theatre is as good as that used to detect the lesion preoperatively.
2. Appreciate that the position of the patient on the operating table is not necessarily the same as in the radiology suite.
3. If specimen ultrasound fails to see the lesion, a rescan in or around the wound can be performed.

In over 1000 such localizations, we have only missed two; both of these patients required re-operations.

Preoperative axillary ultrasound

David Clark
The Breast Centre, Newcastle, NSW, Australia

Notes

From January 2006, to reduce our rate of positive sentinel node biopsies, we began doing targeted axillary ultrasounds on all patients with proven breast cancer. In more than 500 patients evaluated during that time, we reduced our rate of +ve SNB by 70%. Any axillary lymph node that was found to be abnormal was biopsied using a 22-G needle.

In patients who had a high risk of being lymph node positive, as predicted by tumour size, we also biopsied the node that was perhaps most likely to be the sentinel node.

Sonographic findings of abnormal lymph nodes:

Size	Enlarged diameter
Shape	Rounding
Echogenicity	Markedly hypoechoic cortex
Morphologically abnormal	
Cortical thickening	Uniform vs eccentric
Hilar compression	Uniform vs eccentric
Hilar indentation	Convex "rat bite"
Hilar displacement	Present
Hilar obliteration	Present
Loss of echogenic outer	
Capsule & angular margins	Present
Relationship between adjacent	
Lymph nodes	

The important steps for using this method are:

1. High resolution breast ultrasound machine.
2. An experienced, dedicated and patient ultrasonographer.
3. An experienced cytopathologist.
4. An open mind if the lymph node is abnormal but the cytology is benign.

All patients with early breast cancer should have pre-operative targeted axillary ultrasound.

Notes

MINI-SYMPOSIUM: SHOULD WOMEN WITH NEWLY DIAGNOSED BREAST CANCER HAVE MRI STAGING OF THE AFFECTED BREAST?

Sponsored by AstraZeneca Oncology

MRI in staging the breast and axilla

Fiona J Gilbert
University of Aberdeen, Scotland, UK

Multifocal or multicentric disease will be found in histological specimens in up to 20-50% of invasive cancers. A number of studies have demonstrated that MRI will detect additional disease [1-6] and does so with greater accuracy than mammography and ultrasound particularly in women with dense breast tissue. However whether MRI actually impacts on improved patient management by reducing the number of second operations by improving the accuracy of assessing disease extent, or reduces local recurrences and ultimately impacts on survival is not known. A Blue Cross and Blue Shield Association Medical Advisory Panel review published in 2004 concludes that there is insufficient evidence of patient benefit from using MR in staging the breast. The main concerns raised are the potential false positive rate of MRI and the need to biopsy any additional disease found with MRI before subjecting a patient to a mastectomy rather than breast conservation therapy (BCT) with radiotherapy[7].

The Blue Cross review of 18 studies with 1,401 patients found that between 2-15% of patients being considered for BCT might be considered for mastectomy as a result of multicentric disease found on MRI, with women with DCIS or invasive lobular cancer being most likely to have multicentric disease (20-28% and 17-40% respectively) [7]. A more recent meta-analysis of pre-operative MRI found additional disease in 163 of patients. The conversion from wide local excision to mastectomy was 8.1% and from WLE to a wider excision 11.3%. In women in whom the additional was subsequently found to be benign there was a 1.1% increase mastectomy rate and 5.5% had wider excision [8].

The National Institute for Clinical Excellence undertook a literature search to identify evidence for health economic benefit for MRI in pre-operative staging. From 100 references initially identified only one was finally included [9]. This study of 57 patients concluded that MRI was better than mammography in detecting malignancy (98% versus 84%; p=0.03) and the true extent of disease (98% versus 55%; p<0.001) and that possibly financial savings could be made. However this small American study may not be relevant to a UK or European setting. The UK NICE guidance concluded that MRI was not indicated pre-operatively except where patients had dense breasts, the imaging findings were discordant or where the patient had an invasive lobular cancer [10]. Lobular cancers have an infiltrative pattern which are more easily delineated on MRI than by mammography [11,12] and are more likely to be multi focal [13,14].

Staging axillary lymph nodes

Ultrasound is the most commonly used method to assess the axillary lymph nodes. But this technique only has a 50% accuracy unless it is combined with image guided fine needle aspiration for cytology or core biopsy. MRI is not undertaken in routine practice at present. There have been a number of studies to examine the MR accuracy of the detection of abnormal lymph nodes. These studies have had reasonable sensitivities but generally poor specificity. The shape and size of the lymph node has been used but this has been shown to have poor discriminatory value. The degree of contrast enhancement is another parameter to separate benign from malignant disease. The metastatic deposits in the nodes have increased vascularity compared to the normal node [15]. However to date results have been disappointing. Ultra small iron oxide particles (USPIOs) have also been investigated with some promise. These are given intravenously 24 hours prior to imaging. Macrophages in the normal nodes take up the iron oxide particles which appear on a gradient echo sequence as signal drop-out caused by the marked para-magnetic effect. Abnormal nodes do not take up the iron oxide and so remain of intermediate signal. The main problem is the identification of small metastatic deposits within a node.

References

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Notes

Notes

Should women with newly diagnosed breast cancer have MRI staging of the affected breast? A surgical perspective

James French
NSW Breast Cancer Institute, Westmead Hospital, Sydney, NSW, Australia

MRI of the breast now has an established role in screening women who are at high risk of developing breast cancer. Its place in the workup of symptomatic women is less clear and remains controversial. A recent meta-analysis of 44 studies concluded that MRI has high sensitivity and lower specificity in the evaluation of breast lesions[1]. There is now increasing evidence for the usefulness of MRI in the search for an occult primary breast cancer in women presenting with axillary nodal disease due to its relative high sensitivity when compared with conventional imaging modalities[2].

In the context of a woman who has a confirmed diagnosis of early stage breast cancer via conventional triple assessment there is currently no role for the routine use of pre-operative staging MRI of the affected breast to aid in treatment decisions.

It is tempting to assume that, as MRI that has been consistently shown to be more sensitive than conventional breast imaging[2] in its ability to detect multifocal / multicentric cancer, it will provide an accurate map of the extent of disease burden in the breast and thereby act as a guide for the extent of local resection. This ability of MRI to detect additional foci of tumour has then been used to argue the case for its routine use pre-operatively to stage the extent of disease in the affected breast.

Decision to convert from breast conserving surgery to mastectomy on the strength of MRI findings has been reported to occur in up to 25% of patients[3]. In a review article Houssami concluded that MRI staging causes more extensive breast surgery in an important proportion of women by identifying additional cancer. However, there is a need to reduce false positive MRI detection[4].

It is the assumption that a patient has benefited by mastectomy rather than breast conserving surgery + radiotherapy on the basis of multifocal / multicentric disease detected only on MRI, that is open to question.

The paradox is that, to date, there is no evidence to suggest that pre-operative MRI examination leads to improved clinical outcomes. There are now more than 30yrs of clinical data demonstrating the efficacy of breast conserving surgery in combination with radiotherapy which results in acceptably low local recurrence rates for patients who had treatment decisions made on clinical + conventional imaging grounds alone. Fisher reported a local recurrence rate of 14.3% at 20 years for women treated with breast conserving surgery followed by radiotherapy[5].

Solin published a retrospective series of patients with the purpose of determining the relationship of breast MRI to outcome after breast conservation treatment with radiation for women with early stage invasive breast cancer or DCIS. He concluded that the use of preoperative breast MRI was "not associated with an improvement in outcome after BCT with radiation". In his paper local failure rates were the same at 8 years whether or not MRI was used preoperatively to plan breast conservation treatment. In the same paper overall survival was found to be no different[6].

Historical pathological data demonstrates that up to 63%[7] of apparently unifocal tumours (on clinical + conventional imaging grounds) are in fact multifocal or multicentric at the time of diagnosis on histopathology. Despite this fact there are now many decades of data, which demonstrate that local recurrence rates in breast conserving surgery are acceptably low. This occult disease is well treated by the addition of radiotherapy.

Despite its well documented greater sensitivity than conventional breast imaging methods, MRI still fails to detect some cancers. Sardanelli reported that MRI underestimated the extent of disease in 19% of cases and over estimated it in 30% of cases[8].

The high sensitivity and low specificity results in a not insignificant false positive rate, necessitating that all lesions found in addition to the index lesion should be further evaluated with second look ultrasound. When US is focussed on a particular part of the breast, lesions not seen on initial US, but detected on MRI, will often be found. Any such lesion should undergo US guided biopsy to confirm its nature.

When making treatment decisions a surgeon has to take into account many different factors all of which may not be congruent. There are the patient's desires / needs, results of family history and clinical examination, and conventional imaging findings.

In practical terms access to MRI is very varied. Costs in Sydney typically vary from $350-$800. There are inevitable delays that occur with the use of MRI, due to access issues, as well as the need to perform second look US + / - US guide biopsy.

At this stage the routine use of MRI to guide local treatment decisions in the breast cannot be recommended.

In addition to the above information the presentation will include some brief case studies to highlight some of the issues involved.

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Notes

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Pre-operative MRI to "stage" patients with histologically documented primary breast cancer

Daniel F Hayes* [1], Nehmat Houssami [2]

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Randomized controlled trials (RCTs) have shown equivalent survival for women with early stage breast cancer who are treated with breast conservation therapy (BCT: local excision and radiotherapy) or mastectomy. Decades of experience have demonstrated that BCT provides excellent local control based on defined standards of care. Magnetic resonance imaging (MRI) has been introduced in pre-operative staging of the affected breast in women with newly diagnosed breast cancer in the absence of prospective, level I, randomized clinical trial data. The widespread acceptance of "staging" MRI has occurred principally because it detects additional foci of cancer (foci other than the proven index cancer) that are occult on conventional imaging. It has been assumed that this increased detection of additional sites would lead to improved clinical outcomes for one of two reasons: 1) it would permit better pre-surgical planning and therefore lower the need for re-excision, or 2) it will improve long term outcomes by decreasing local-regional recurrences and, perhaps, long term metastases.

The median incremental (additional) detection for MRI has been estimated as 16% in meta-analysis[1]. Evidence consistently shows that MRI *changes* surgical management, usually from breast conservation to more radical surgery (mostly mastectomy), However there is no evidence that it *improves* surgical care or prognosis. Results reported in abstract form only from a randomized clinical trial designed to demonstrate lower re-excision rates have, so far, been negative[2]. Local-regional "in-breast" recurrence rates are <5% in most major medical centers using classical radiologic and pathologic evaluation. Thus, although MRI staging might decrease this already low incidence of ipsilateral breast recurrence rates, the high rate of detection suggests that many cancers identified by MRI are adequately treated with whole breast radiation. Taken together, available data indicate that MRI does not reduce re-excision rates and that it causes false technical and, importantly, biological, positive findings, leading to unnecessary and disfiguring additional surgery[3].

RCTs are needed to establish the clinical, psychosocial, and long-term effects of MRI (including its impact on the contralateral breast) and related change in treatment from standard care in women newly affected by breast cancer.

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A radiation oncology perspective

Lizbeth Kenny
Royal Brisbane and Women's Hospital, Brisbane, Qld, Australia

Notes

Locoregional control is of major importance in women with breast cancer. Not only does post operative radiation treatment improve locoregional control in all women but this also translates into a survival benefit. Locoregional recurrence hence has a negative impact on women in every regard. Knowing as much as possible about the extent of disease in the breast at diagnosis allows for a more clear management pathway as far as locoregional treatment is concerned, both for surgery and radiation treatment. Surgical clearance of known macroscopic disease is highly desirable. Involved margins are an important predictor of in-breast recurrence. MRI scans offer an important opportunity in selected women to better appreciate the extent of breast cancer pre-operatively and are of major importance in assessing previously unappreciated multifocality. Unappreciated multifocal disease is likely to lead to an increased risk of relapse even after breast radiotherapy and subsequent detriment to the individual woman.

MRI scans therefore can influence the extent of surgery prior to radiation treatment influencing significantly the chance of locoregional control which with sufficient passage of time is likely to influence survival.

Women most likely to benefit are women where mammography has been unhelpful in displaying the index cancer, younger women with dense breasts, or in women where there is a significant risk of bilateral breast cancer. Having as clear a picture as possible about the extent of disease in the breast will be of benefit in planning definitive locoregional surgery and radiation treatment with the aim of maximizing locoregional control with all its attendant benefits.

Sponsored by AstraZeneca Oncology

Notes

Breast carcinoma in the elderly: Is it different?

Jean F Simpson
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Breast cancer is the most common cancer in North American women and age remains a strong risk factor for the development of new breast cancer. The estimated risk of developing breast cancer for women aged 60 to 79 is 1 in 14, compared with a risk of 1 in 24 for women 40 to 59 years of age; the risk for women younger than 39 is 1 in 228.[1] Almost half of newly diagnosed breast cancers are diagnosed in women older than age 65, and approximately one third occur in women over the age of 70.

Concurrent with the age related increased risk of developing breast cancer, there is also an increase in the age of the population. Thirty years ago, people older than 65 represented just over 11% of the total population of the United States, and this age bracket is expected to represent 20% of the population by the year 2030. These issues related to aging have important implications for the decisions regarding screening mammography, treatment of primary carcinomas, and the use of systemic adjuvant therapy.

Breast cancer is both the most common cancer and cancer cause of death in Australian women.[2] There are more new breast cancers diagnosed in women 70 years or older compared with women younger than 50 in Australia. Although breast cancer tends to have more favorable biologic characteristics in older patients, age adjusted and stage adjusted survival are similar in older and younger women with the exception of the very young (younger than 35) and the very old (> 85 years old). A thoughtful review of some of the management issues of early stage breast cancer in elderly women has been presented by Passage and McCarthy[2].

Despite breast carcinoma being very common in elderly women, there is substantial evidence that older women are less likely to receive standard care for their disease. There are multiple factors related to this under-treatment, including accrual of few elderly patients to clinical trials, physician and family bias that the patient will not tolerate standard treatment, consideration of natural life expectancy and greater risk of toxicity.

Much of the research related to breast cancer has focused on younger patients. Few studies of the pathologic features of breast cancer in the elderly are available. A well documented large series from a single center has been presented by Cheung et al.[3] from the University of Nottingham, in the United Kingdom. Almost 2000 invasive breast carcinomas diagnosed between 1987 and 2006 were the subject of this paper. Histologic features and estrogen receptor status of carcinomas present in the elderly were compared to those of younger counterparts treated in the same time frame. Importantly, careful histology assessment was performed by a single pathologist. In this series "elderly" was defined as women over the age of 70. The histologic type most represented in this series was invasive ductal carcinoma, no special type (87%) with 3% of cases being pure mucinous carcinoma. The elderly patients were more likely to be diagnosed with carcinomas that were of intermediate combined histologic grade (Grade 2) and strong expressers of estrogen receptor compared with younger women who were more likely to have Grade 3, estrogen receptor negative breast cancers.

A large data set evaluating the characteristics of invasive breast carcinomas in the elderly comes from a review of the San Antonio Breast Cancer Database and the Surveillance Epidemiology, and End Results Registry.[4] Although this review has the advantage of very large numbers of patients, careful central pathology review is not a feature of these registries. Regardless, in older patients, there was an association between the presence of more favorable characteristics of the tumor, including estrogen receptor positivity, low proliferation rate, and the lack of over expression of her2/neu. With elderly patients who presented with lymph node negative and/or small carcinomas, the expected and observed survival were almost identical. An earlier publication from the San Antonio Breast Cancer Database presented a comprehensive clinical and biologic characterization of tubular and mucinous carcinomas along with patient outcome. Not unexpectedly, disease-free and overall survival were better for patients with tubular and mucinous carcinomas compared with women who had carcinomas of no special type. Tubular and mucinous carcinomas occurred more frequently in older women, with 71 years being the average age at diagnosis for women with mucinous carcinoma.[5]

In summary, the somewhat favorable histologic and biologic parameters of invasive breast carcinoma diagnosed in the elderly may allow for treatment options that permit a balance between coexisting morbidities, life expectancy, and quality of life.

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Notes

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Should elderly women have full surgery?

Nigel Sacks
University of Adelaide, SA, Australia

In Australia, 26% all breast cancers occur in women aged 70 and over and in this age group the disease has a 6-fold higher incidence and a >8-fold higher mortality than their younger cohort. Women aged 70 and over currently account for 12% of the total Australian population but it is estimated that by 2030 this figure will be close to 25%. The term "elderly" should be defined as age 70 and over as the prevalence of age related changes is represented by a near flat line up to the age of 70 and increases sharply after this. In the past, due to a combination lack of data, misconceptions and misinformation elderly women have been less likely to receive breast conserving surgery, axillary node dissection, radiotherapy, chemotherapy, definitive primary and guideline therapy. The aim of this paper is to establish whether or not elderly patients should receive optimal standard surgery ("full surgery") or not.

Treatment in this age group has for years been influenced by a number of misconceptions. Whilst it is true that the presence of co-morbid illness increases with age; 35% of 70-79 year olds have at least 2 co-morbid illnesses, the average actuarial survival for an 80 year old is 12 years. Relatively little is known about evidence based surgical care in this age group as they have been largely excluded from randomised trials despite the fact that they want to take part, poor drug compliance, treatment toxicity and the misconception about the lack of breast surgical morbidity in the elderly. Breast tumours in his age group do tend to be of lower grade, more often ER +ve and HER 2 -ve, present at a later stage and age is of itself an independent prognostic factor.

One of the key challenges for the treating doctor is to accurately estimate the older patient's individual health status. This can be done using the "gold standard" Comprehensive Geriatric Assessment (CGA) or a simpler tool such as the daily living or co-morbidity scale or mini mental-state evaluation. The major factor affecting surgical morbidity is not age itself but the presence of significant co-morbidity and all the available evidence confirms that breast surgery is in fact just as safe in the elderly. Sadly,a small trial of nonsurgical primary endocrine therapy in Scotland in the 1990s denied optimal surgical care to the elderly in Europe for many years. A recent Cochrane overview confirmed that such primary endocrine therapy was associated with a worse outcome and survival than primary surgery; primary endocrine with an aromatose inhibitor should therefore be limited to patients with ER +ve tumours who refuse or are too unfit for surgery.

Just as in the case with younger patients, elderly patients prefer breast conserving surgery to mastectomy with its indications the same in both age groups. In the EORTC 10850 trial patients were randomised to wide excision and Tamoxifen versus mastectomy and no Tamoxifen! After 10 year follow up, overall survival was the same with local relapse worse in the lumpectomy group (26 vs 16%). An important study by Hughes et al limited women 70 and over with ER +ve T1 tumours randomised breast radiotherapy after lumpectomy with only a 6% (1 v 7%) reduction in locoregional recurrence at 8.2 years follow up and no difference in disease-fee or overall survival.

Surgical treatment of the axilla is slightly more complicated. In those with preoperatively confirmed positive axillary disease, full axillary dissection is the preferred option with a proven overall survival benefit of 6-16%. In patients with a negative axilla there is a genuine choice. Axillary sentinel node biopsy is a well proven, reliable and safe staging procedure in this age group but if the patient is not eligible for adjuvant chemotherapy a conservative approach may be acceptable and preferable to both patient and surgeon. Age should be no barrier to breast reconstruction but elderly women are less likely to undergo reconstruction due to a combination of physician preference/bias, patient fear of complications, perception of being "too old", and unfounded fear concerning the effect of reconstruction on relapse.

In conclusion, elderly patients should not be denied optimal standard surgical care except in the careful selected subgroups outlined above. Hopefully this group of patients will benefit from participation in ongoing and future trials such as the ongoing Perioperative Endocrine Therapy (POETIC) trial.

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Tailoring radiotherapy for elderly women

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Notes

The incidence of breast cancer increases with increasing age. Life expectancy in western societies is increasing and so it is expected that there will be a major increase in breast cancer in the older population.

Older women with breast cancer tend to have tumours with less aggressive biologic characteristics. They tend to be of lower histologic grade and are more likely to be oestrogen receptor positive and HER2 negative.

With increasing age, there also comes increasing co-morbidities, poorer functional status and increasing disabilities. This in turn leads to a higher risk of treatment-related complications and mortality.

Thus, with differing patient related factors and tumour related factors, to a younger population of women, thought needs to be given to tailoring treatment recommendations to the older population. Research focused on this older group of women however has been minimal, so there is little to guide the clinician in this tailoring process.

Breast conserving therapy is a routine treatment in women with operable breast cancer. It has been well established that radiation treatment to the breast after breast conserving surgery is optimal management, providing the lowest local recurrence rates[1]. To date, no subset of women with low risk disease has been defined in whom radiation can be omitted without compromising local control.

For an older woman, six weeks of radiation treatment post-lumpectomy may be a daunting proposition and for those with other co-morbidities may be exhausting and detrimentally affect their quality of life. This raises the question of whether radiation can be omitted in some older women with favourable tumours.

A retrospective study of nearly 5000 women addressing this question has shown however that omitting radiation was associated with significantly reduced local control, breast cancer specific survival and overall survival [2]. The conclusion from this was therefore that local therapy was inadequate when radiation was omitted, and that radiation should continue to be a standard part of breast conserving therapy in the elderly, unless of course the woman had significant co-morbidities and her longevity was likely to be short.

In the United Kingdom, a prospective randomised trial is under way looking at the value of postoperative radiotherapy in minimum risk elderly women – the PRIME Trial. Patients over 65 years were eligible to be randomised to radiation or no radiation post-lumpectomy, provided the tumour was favourable and oestrogen receptor positive. The end points being measured will be quality of life, anxiety and depression and cost effectiveness, as well as recurrence rates, functional status, treatment related morbidity and cosmesis[3]. Results of this will provide important guidance in management of early breast cancer in elderly women.

Other than omission of radiation, there are other ways of tailoring a programme of postoperative radiation which may be more acceptable to and tolerable for an elderly woman.

One way of tailoring radiation if it is deemed necessary, is to shorten the overall treatment programme from the standard five to six weeks, using a hypofractionated radiation schedule. This has been investigated in a Canadian prospective randomised clinical trial, allocating women to either have 50Gy in 25 fractions over 35 days or 42.5Gy in 16 fractions over 22 days[4]. The shorter 16 fraction schedule was shown to have equivalent five year local recurrence free survival, overall survival, cosmetic outcomes and toxicities to the longer treatment course. The shorter programme may obviously be logistically more acceptable to an elderly woman.

Partial breast radiotherapy also has advantages to the older women with both shorter treatment schedules and potentially less toxicity. The fundamental concept behind partial breast radiation is that more than 70% of ipsilateral breast tumour recurrences occur in the vicinity of the original tumour. Several techniques can be used including intraoperative treatment, interstitial brachytherapy or 3D conformal radiation treatment given postoperatively in an accelerated fashion[5]. These techniques may be suitable for many elderly women with small, unifocal, Grade I, oestrogen receptor positive tumours.

Treatment decisions in the older woman, including the use of radiation treatment and how it is given, need to be tailored by taking into account co-morbidities and life expectancy, together with functional and quality of life outcomes from treatment. There is little evidence in current modern clinical trials to help in treatment decision making in this important group of women, and this is an area that needs to be addressed in the future.

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Is chemotherapy contra-indicated in elderly women?

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Four decades of randomized clinical trial data have demonstrated that adjuvant systemic therapy clearly results in mortality reduction, and great survival, in non-metastatic breast cancer[1]. However, it is clear that not all women benefit from AST, especially chemotherapy. Personalization of chemotherapy can be accomplished with two considerations: Prognosis and Prediction. In general, prognosis is determined by clinical and pathologic review of regional lymph nodes, especially axillary, and tumor status, including evidence of skin or dermal lymphatic invasion clinically and pathologic tumor sizing. Decisions regarding chemotherapy have been mostly based on whether a patient either has clinical or pathologic evidence of a moderate to high risk of subsequent recurrence.

Until recently few if any biologic subgroups were identified that might predict whether chemotherapy would or would not be of benefit. Indeed, the only proposed biologic factor to do so has been age. In early studies of adjuvant chemotherapy, arbitrary subgroup analysis of age < or > 50 suggested limited if any benefit in the latter group of patients[2,3]. However, subsequent studies have shown a clear, although step-wise decreased, benefit for chemotherapy in the 6th and 7th decades.

What is the reason behind this curious observation? Several theories have been put forth, including arbitrary dose reductions to avoid toxicities, higher rates of toxicities due to co-morbidities, and higher rates of non-breast cancer related mortality[4]. Although all of these have merit, perhaps the most plausible explanation is the difference in tumor and host biology between older and younger women with breast cancer. In general, breast cancer in older women tends to be lower grade, and have higher levels of estrogen receptor (ER), progesterone receptor, and lower levels of proliferation indices and HER2 expression. All of these imply better overall prognosis and high rates of benefit from anti-estrogen therapy, but they may be associated with relative resistance to chemotherapy[5,6].

Precious little data has been generated regarding the benefits of AST for septageneric or older women. Few trials have included such women, and almost none has been conducted specifically addressing them. A retrospective analysis of the Oxford Meta-analysis data has demonstrated that, regardless of age, women with ER negative breast cancer appear to benefit from chemotherapy equally[7]. Importantly, a recently published report from CALGB and the US Intergroup has demonstrated that combination chemotherapy (AC or CMF) is more effective than single agent capecitabine in women over 65 years[8].

Taken together, these data suggest that age, per se, is not as important a consideration as biology of the cancer and health status of the patient. Oncologists should consider both and make thoughtful decisions regarding recommendations for adjuvant chemotherapy for older women with early stage breast cancer.

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Is there a role for computer-aided detection in screening?

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Worldwide, more than a million women are diagnosed with breast cancer every year, and breast cancer is the second most common cause of cancer-related deaths in women. The efficacy of breast screening in reducing breast cancer mortality and improving the prognosis of the disease through early detection has been demonstrated in several large scale clinical trials. The UK was one of the first countries to establish a national breast screening programme offering free mammography screening once every three years to women aged 50-64 years.

Independent double reading of mammograms with arbitration (or consensus) is the 'gold standard' and has been shown to improve cancer detection rates by up to 10%, and small cancer detection rate by 24%. A second reader detects an additional 10% of cancers that have been overlooked by the first reader. However, even with double reading, up to 25% of interval cancers and 19% of incident round cancers are found to have a detectable lesion on the prior screening mammogram that was overlooked or dismissed by both readers. The practice of double reading with arbitration or consensus is time consuming and has cost and manpower implications for screening programmes that are struggling to cope with the workload of screening the post-war 'baby-boomer' generation and/or extension of the age range for screening. To address the increase in workload, screening programmes have been seeking alternative working practices. Radiographers are being trained to be film readers and the potential of computer aided detection (CAD) technology is being evaluated.

Computer aided detection (CAD) systems were developed to assist film readers improve their performance. CAD systems analyse digital mammographic images using computer algorithms developed to specifically detect abnormalities such as soft tissue masses or microcalcification clusters [1]. The software system identifies and marks potentially suspicious features on a mammogram to attract the reader's attention to any regions that may have been overlooked or dismissed as normal. In practice, the reader would review the unmarked mammogram then reassesses any regions marked by CAD before making a decision on whether or not to recall the case for further investigation. Although sensitivities of up to 88% have been reported for soft tissue masses and 97% for calcifications, CAD systems have relatively low specificity. Readers have to discriminate between numerous false positive CAD marks and true positives that require further evaluation. A high ratio of false positive to true positive marks could reduce a reader's confidence and would be detrimental if they distracted the reader's attention to a genuine abnormality. This has been highlighted as a major limitation to their use in a high volume screening environment where <1% of cases are cancer cases. The early studies with CAD focussed on retrospective evaluations. These had major design weaknesses that limit any generalization of the results to the prospective setting of a screening programme [2]. Most studies used a case mix containing a high proportion of cancer cases which is unrepresentative of the case mix that would be encountered in screening conditions and could overestimate the contribution of CAD prompting. Readers would also be aware that their findings will not have any clinical implications and in some studies readers lacked sufficient training in the use of CAD [3]. Meta analyses of prospective evaluations of CAD comparing single reading and single reading with CAD, and comparisons of single reading and double reading, concluded that there was no significant difference in the cancer detection rate between single reading with CAD and double reading with arbitration [4]. However, single reading with CAD incurred a significantly higher recall rate. The potential benefit of CAD in screening mammography has been a controversial issue [5] and screening programmes considering the utility of CAD require more robust evidence from prospective studies and preferably large scale, randomised trials [6].

CADET II was a multicentre, prospective evaluation of CAD in the UK Breast Screening Programme [7]. This was an equivalence trial with matched pair comparisons of the cancer detection rate and recall rate of single reading using CAD and standard double reading. Participants were recruited from women attending routine two-view mammography at three UK screening centres. 28,204 women were randomised to have their mammograms read by both double reading and by another single reader using CAD. To minimise reader bias, an additional 1152 mammograms were randomised to double reading only and 1182 mammograms to single reader using CAD only. There was no significant difference in cancer detection rate between single reading with CAD and double reading and although the recall rate for single reading with CAD was slightly higher than that for double reading, it was still within the acceptable limit for the UK screening programme. The results of CADET II indicated that CAD could provide an alternative to double reading.

There are several potential benefits in using CAD in screening mammography. CAD could increase the capacity of film reading personnel or provide an alternative work practice for screening programmes using double reading and facing an increase in workload. In screening programmes where single reading is standard practice CAD could raise the performance of a single reader to that of double reading. Improvements in CAD algorithms should continue to increase the specificity of CAD marking and the transition from film screen to digital mammography systems will facilitate the integration of CAD technology into digital workstations and remove the need for separate digitisation of films. However, a formal health economic assessment is required to determine if implementation of CAD and the costs resulting from an increase in assessment clinics justifies the potential savings in reader time.

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Keynote address: The "continuum" from benign to malignant breast disease

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Ever since the mid-1980s, when histologic risk factors for the development of breast carcinoma were well defined, there has been a desire to refine these risks. The original presentation[1] and subsequent epidemiologic studies[2-4] have established differing risks for developing breast cancer based on reproducible histologic changes. While these studies are powerful from an epidemiologic point of view, the results cannot be applied to an individual patient.

One so-called pre-malignant change, atypical ductal hyperplasia (ADH), has been the subject of considerable study as a precursor of invasive carcinoma. Unfortunately, the adenoma-carcinoma sequence that is well accepted in the colon cannot be applied to ADH in the breast. Atypical ductal hyperplasia indicates an increased risk of subsequent development of invasive breast carcinoma in the range of 4 to 5 times that of age-matched controls, and the risk is almost equally bilateral.[1] The fact that subsequent cancers are as likely to develop in the contralateral breast as they are in the breast that contained ADH is argues that ADH is not necessarily a precursor lesion.

Attempts at molecular analysis of atypical ductal hyperplasia have been challenging because of the very focal nature of the lesion. There are genetic changes common to atypical ductal hyperplasia and low-grade ductal carcinoma in situ.[5] The difficulty with these studies is that the cases often have a more advanced lesion present, thus the nature of pure ADH is less certain. This approach does show increasing molecular alterations that parallel morphologic changes, but does not establish ADH as a precursor lesion. Lacking are studies that characterize ADH at a molecular level in the absence of a more significant lesion that also show long-term follow-up. Ideally such studies would identify molecular changes that refine the current understanding of the relative risk of cancer development.

There is an established precursor for invasive breast carcinoma, and that is ductal carcinoma in situ (DCIS). The natural history of ductal carcinoma in situ is that as many as 30% of women with DCIS will eventually develop an invasive breast carcinoma in the same breast (and often in the same quadrant) in which the original diagnosis of DCIS was made. Interestingly, the invasive carcinoma may develop many years after the initial DCIS diagnosis.[6]

As a precursor to invasive carcinoma, DCIS is well established. Attempts at establishing a precursor lesion for DCIS, however, have largely been unsuccessful. There have been reports of columnar cell lesions associated with more advanced lesions, albeit of low grade.[7] Columnar cell lesions by themselves do not confer clinically meaningful increased risk for later cancer development.[8]

The natural history of low grade ductal carcinoma in situ (DCIS) has been established by two series published over 20 years ago.[6, 9] Recently, the Harvard Nurses' Health Study provided additional support for the natural history of DCIS.[10] Thirteen originally diagnosed as benign were reclassified as DCIS after review of 1877 patients. Six of the 13 developed invasive carcinoma and 4 had persistence of DCIS, all in the ipsilateral breast. This ipsilateral recurrence is similar to the findings of Page, et al. in that some invasive carcinomas develop many years after the initial DCIS diagnosis.[6, 11] Unlike the original studies of Page, et al. that included only cases of low grade DCIS, the cases of the Nurses' Health Study included low, intermediate, and high grade DCIS. Not surprising, the invasive carcinomas that occurred after high grade DCIS did so within 5 years, compared with the much longer interval for low and intermediate grade DCIS. These studies all support DCIS as a precursor for invasive carcinoma; it is important to remember that in these series DCIS was diagnosed retrospectively and there was no attempt at clear margins.

Molecular studies of DCIS have shown characteristics in common between DCIS and invasive carcinoma lending more support for DCIS as a precursor. From the Nurses' Health Study, gene expression of DCIS was found to be heterogeneous at a molecular level and there were significant differences between the molecular phenotype of DCIS compared with adjacent invasive carcinomas. High grade DCIS was more likely to be HER2 type and basal-like than lower grade DCIS, lending credence to the theory that high grade DCIS is an obligate precursor of invasive carcinoma.[12, 13] Using laser assisted micro-dissection and a panel of 52 satellite markers, Ellsworth, et al. showed lower levels of allelic imbalance in low grade ductal carcinoma in situ compared with invasive carcinoma. However, allelic imbalance was similar between high grade DCIS and high grade carcinoma,[14] further evidence that high grade DCIS is an obligate precursor for invasion, while low grade DCIS is not necessarily a committed precursor.

Lobular neoplasia, specifically lobular carcinoma in situ, is a well established risk factor for the development of invasive carcinoma, and the earliest description and implied precursor nature comes from the 1940s. The histologic similarity of the characteristic neoplastic cells within lobular units are identical to those of invasive lobular carcinoma, hence the assumption that lobular carcinoma in situ was a precursor lesion. Subsequent studies of lobular neoplasia, both

LCIS and atypical lobular hyperplasia, through long-term follow-up studies, have shown that lobular neoplasia is an indicator of increased risk which is bilateral, again discrediting the lesion as a proven precursor.[15]

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Cryoablation therapy in benign and malignant disease

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The expanded use of improved screening techniques has allowed for the detection of many breast cancers as small tumors at the earliest stages of disease. The complete eradication of tumor is required for optimal local control, however, lumpectomy, as a component of breast conservation therapy, often removes significant amounts of normal tissue that may not be a necessary component of local-regional control and can lead to poor cosmetic outcomes. Percutaneous ablation is currently being investigated as a potential alternative to standard surgical resection for the treatment of early stage breast cancer. To date, there are no large trials that have been performed to prove the efficacy of this technique in breast cancer treatment, however there are several small, single institution and multicenter trials that have documented its ability to eradicate tumor cells with minimal architectural distortion and pain. Ablative techniques have also been well documented for the eradication of malignant disease in other organ systems.

Percutaneous ablation uses thermal changes to coagulate or freeze tumor cells in order to cause the destruction of the undesirable cells. The minimally invasive techniques that have been described include radiofrequency ablation, cryoablation, microwave ablation, interstitial laser therapy, and high-intensity focused ultrasonography (HIFU) ablation. This review will focus on briefly describing the use of cryoablation therapy for benign and malignant disease of the breast, the benefits and disadvantages, and current evidence supporting the technique.

General considerations

Prior to any ablative procedure, a core needle biopsy is required for accurate diagnosis of the breast mass and to allow for assessment of tumor markers that can impact therapy of malignant disease such as estrogen receptor, progesterone receptor, and HER2 protein receptor status. Additionally, radiographic studies in the form of ultrasonography, diagnostic mammography, or magnetic resonance imaging (MRI) are essential for appropriate screening prior to the ablative therapy. Pre-ablation assessment should include an analysis of tumor volume and location and the identification of neighboring anatomic structures including blood vessels and overlying skin.

Technical considerations

After a breast mass is fully assessed, a local anesthetic can be applied to the overlying skin prior to probe placement. The surgeon then makes a small skin incision to allow for placement of the ablation probe directly into the tumor under radiologic guidance. During cryoablation, the cryoprobe is ideally guided into the center of the targeted lesion. Cooling gas (argon, nitrogen, or liquid nitrogen) flows into the probe tip and causes a local freezing phenomenon. Usually 2 or 3 freeze/thaw cycles are employed in an attempt to eradicate the tumor cells. The surgeon can monitor the thermal changes in the targeted tumor bed during the procedure. Current protocols require surgical removal of malignant tumors after cryoablation, as the safety and efficacy is still being assessed. However, percutaneous ablation can replace the need for lumpectomy of benign tumors such as fibroadenomas. Post-ablation radiologic assessment is important to assess for residual or untreated tumor and is one of the major outcomes being evaluated in ongoing clinical trials.

Cryoablation attacks the tumor cells by direct cell injury. This occurs when cells closest to the cryoprobe form intracellular ice, leading to shearing of the cell membranes. Farther away from the cryoprobe, the tumor cells are frozen more slowly and the ice forms extracellularly, creating a hypertonic extracellular environment. Osmotic shifts drive the water out of cells, causing dehydration and cell membrane damage. During the thawing cycle, water will rush back into the cells secondary to the relative hypotonicity of the extracellular environment; this results in intracellular edema and lysis.

A second effect of cryoablation on tumor tissues is vascular in nature. The initial freeze causes vasoconstriction leading to a relative decrease in blood flow with anoxia. This damages the capillary endothelium, which ultimately causes leakage, thrombosis, and target-tissue anoxia. As the blood vessels thaw, a compensatory vasodilation with resultant hyperperfusion, further exacerbates endothelial damage over several days.

Clinical trial results

Cryoablation has long been applied in the treatment of prostate cancer and metastatic disease to the liver, however, the use of cryoablation in breast cancer is relatively new. Kaufman and colleagues published 2.6-year follow-up of cryoablation for benign fibroadenomas of the breast. In this multi-institutional trial, 57 patients were treated with cryoablation. Of the tumors that were palpable at presentation, only 16% remained palpable following cryoablation. At 2.6 years, a median volume reduction of 99% was revealed by ultrasonographic follow-up. Fibroadenomas that were larger than 2 cm resolved more slowly.

Pfleiderer et al. published an initial pilot study of 15 breast cancer patients with T1or T2 tumors who underwent cryoablation. Sixteen tumors were treated with 2 freeze-thaw cycles with a minimum freeze cycle temperature of –146°C. At surgical resection 5 days after cryoablation, 5 tumors were smaller than 1.5 cm and showed no remaining invasive carcinoma. Two showed DCIS adjacent to the cryoablated lesion. Eleven tumors were 1.6 cm or larger and showed remnants of invasive carcinoma with subtotal necrosis on H&E stained sections.

Pfleiderer et al. recently published a larger trial of 30 patients with tumors 1.5 cm or less in size. Twenty-nine patients had successful cryoablation and histologic review after resection revealed no viable tumor within the cryoablated lesion. DCIS was found beyond the margins of the cryolesions in 5 of 29 patients. One patient suffered arterial hemorrhaging after the cryoprobe was removed.

Sabel et al. published a multicenter, phase I trial in which 27 patients with confirmed T1 breast cancers underwent ultrasonographic-guided cryoablation. Continuous ultrasonography was utilized during the procedure to analyze the ice ball around the cryoprobe. Surgical resection was performed within 4 weeks of cryoablation. Average tumor size was 1.2 cm and histologic evaluation revealed no viable invasive cancer in 84% of patients. As with previous studies, DCIS was found adjacent to the treatment zone. Tumors smaller than 1 cm were more likely to be completely ablated and 63% of the tumors smaller that were 1.5 cm were completely ablated. Cryoablation did not have an impact on the use of sentinel lymph node surgery.

Morin et al. also published a small phase I study of 25 patients with T1and T2 breast tumors treated with cryoablation. In this study, MRI-guided cryosurgery was assessed and mammography, ultrasonography, scintimammography, and MRI were performed before and after the cryoablation procedure. There were 13 cases that were deemed to be completely ablated with no viable tumor cells in the surgically resected specimen. This study was too small to make definitive conclusions but attempted to use pre and post-ablation imaging in order to assess the success of the cryoablative procedure.

Cryotherapy has multiple potential benefits. First, it is a procedure that can be performed wholly in the outpatient setting. The anesthetic effects of freezing allow this procedure to be performed with minimal use of local anesthetics and minimal to no postoperative analgesics. Additionally, large-scale trials have validated the safety and efficacy of cryoablation for other organ systems. Finally, as the ice ball is visible on ultrasonography, this allows a means of approximating the distribution of tissue encompassed in the ice ball. Compared with the electrode used in RFA, which conducts heat unevenly and leads to irregular necrosis throughout the tumor, the cryoprobe used in cryoablation allows for even temperature distribution and thus a uniform, symmetrical cytotoxic effect on the targeted tumor. Also, while RFA requires a minimum distance of 1 cm between the tumor and the skin to minimize burn risk, cryoablation, does not require this distance, as an injection of sterile saline can be used to increase the distance between the tumor and the skin to prevent damage caused by the ice ball.

There are limitations to the cryoablation procedure. Since total ultrasound reflection occurs at the ice interface, no structure is visible beyond the ice ball. It is therefore, difficult to assess the exact dimensions of the ice ball when ultrasonography is used for monitoring. This might be avoided by using MRI instead of ultrasonography. Another potential difficulty is the fact that the ice ball persists for up to 1 month after the procedure. This can obscure both physical examination and radiologic interpretations. There have not been any large-scale trials performed to test the efficacy of cryoablation for the treatment of early-stage breast cancer. The American College of Surgeons Oncology Group has recently opened a phase II trial to determine the rate of complete tumor ablation in breast cancer patients treated with cryoablation (ACOSOG Z1072). Secondary objectives of this trial include evaluating the negative predictive value of MRI in the post-ablation setting to determine residual invasive ductal carcinoma or DCIS.

Conclusions

Compared with surgery, a minimally invasive approach with cryoablation for the treatment of breast cancer is a technique that can result in decreased pain, less disfigurement, and reduced medical costs. However, until imaging studies can reliably predict which tumors have been completely ablated, surgeons must still rely on post-ablation resection to adequately assess the presence of residual tumor. All important pathologic determinations need to be made prior to the ablative procedure in order to assure appropriate delivery of adjuvant therapies. The interaction of radiation therapy with the post-ablative tissue is yet to be determined with respect to follow-up imaging and cosmesis. The success of the ablative procedure relies not only on the ability of radiologic imaging modalities to determine the extent of residual disease following ablation but also on the expertise of the person performing and interpreting the study.

Notes

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Decision making in immediate breast reconstruction

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Notes

Decision making for immediate breast reconstruction usually takes place in the context of an acute cancer diagnosis. Women and their specialists need to consider multiple complex issues within a short time frame, while also dealing with the psychological and therapeutic implications of the cancer diagnosis itself. Factors that need to be considered when discussing reconstruction include whether a unilateral or bilateral procedure is planned, and patient suitability for autologous or prosthetic reconstruction. The surgeon and patient need to discuss the likelihood of a contralateral procedure being required for symmetry, and the women's satisfaction with her current breast size and shape. It may be important to consider the family history, and the risks and benefits of performing a contralateral prophylactic mastectomy for a woman with unilateral disease. The feasibility and safety, both oncological and in terms of wound healing, of skin sparing and subcutaneous mastectomy also need to be considered [1,2].

More fundamentally, even the decision to offer reconstruction at all, or whether to perform delayed or immediate reconstruction can be difficult. Many surgeons are reluctant to offer breast reconstruction to women with co-morbidities such as obesity and smoking because of evidence of increased complications in these groups [3]. Other surgeons may not offer immediate reconstruction to women who are likely to need post operative chemotherapy because of concerns about the potential for delay in commencement of treatment, although this has largely not been substantiated in the literature [4]. There is however a consensus that post reconstruction radiotherapy results in a higher complication rate and poorer cosmetic outcome [5,6], and many surgeons avoid immediate reconstruction in women likely to need post mastectomy radiotherapy. It can be difficult for a surgeon to accurately predict which women may need post mastectomy radiotherapy; factors available to the surgeon preoperatively may include MRI, axillary ultrasound and biopsy, and even breast cancer excision and sentinel node biopsy in addition to the usual imaging and biopsy techniques. A prospective study is currently underway at the Royal Adelaide Hospital, with the aim of assessing which parameters are used by surgeons when making recommendations for the timing of breast reconstruction, and which factors may best predict for the need for post mastectomy radiotherapy.

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Notes

Prediction of local recurrence, distant metastases and death following breast-conserving therapy in early-stage invasive breast cancer using a five biomarker panel

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Background and purpose

To determine the clinical utility of intrinsic molecular phenotype after breast-conserving therapy (BCT) with lumpectomy and whole breast irradiation with or without a cavity boost.

Patients and methods

498 patients with invasive breast cancer were enrolled into a randomised trial of BCT with or without a tumor bed radiation boost. Tumors were classified by intrinsic molecular phenotype as luminal A or B, HER-2, basal-like or unclassified using a 5 biomarker panel: ER, PR, HER-2, CK5/6 and EGFR. Kaplan-Meier and Cox proportional hazards methodology were used to ascertain relationships to ipsilateral breast tumor recurrence (IBTR), locoregional recurrence (LRR), distant disease free survival (DDFS) and death from breast cancer.

Results

Median follow-up was 84 months. 394 patients were luminal A, 23 luminal B, 52 basal, 13 HER-2 and 16 unclassified. There were 24 (4.8%) IBTR, 35 (7%) LRR, 47 (9.4%) distant metastases and 37 (7.4%) breast cancer deaths. The overall 5-year disease-free rates for the whole cohort were: IBTR 97.4%, LRR 95.6%, DDFS 92.9% and breast cancer-specific death 96.3%. A significant difference was observed for survival between subtypes for LRR (p=0.012), DDFS (p=0.0035) and breast cancer-specific death (p=0.0482) but not for IBTR (p=0.346).

Conclusions

The 5-year and 10 year survival rates varied according to molecular subtype. Although this approach provides additional information to predict time to IBTR, LRR, DDFS and death from breast cancer, its predictive power is less than that of traditional pathological indices. This information may be useful in discussing outcomes and planning management with patients after BCT.

Meta-analysis of preoperative contralateral MRI in women newly diagnosed with invasive breast cancer

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*Brennan ME, Houssami N, Lord SJ, Macaskill , Irwig L, Dixon JM, Warren RM, Ciatto S. Magnetic Resonance Imaging Screening of the Contralateral Breast in Women with Newly Diagnosed Breast Cancer: Systematic Review and Meta-Analysis of Incremental Cancer Detection and Impact on Surgical Management. *J Clin Oncol* (in press.)

Background and purpose

Pre-operative magnetic resonance imaging (MRI) is increasingly used for local staging in women with breast cancer.[1] This includes screening the contralateral breast for cancer occult to conventional imaging with mammogram and ultrasound. We present a meta-analysis of studies reporting contralateral MRI in women with newly diagnosed invasive breast cancer.

Methods

We systematically review the evidence on contralateral MRI, calculating pooled estimates for positive predictive value (PPV), true positive: false positive ratio (TP: FP) and incremental cancer detection rate (ICDR) over conventional imaging. Random effects logistic regression examines whether estimates are associated with study quality or clinical variables.[1] We also report the characteristics of MRI-detected cancers, and the associated impact on treatment.

Results

Twenty two studies reported contralateral malignancies detected only by MRI in 131 of 3253 women. MRI identified suspicious findings in 9.3% of cases. Incremental cancer detection rate (cancers detected on MRI, not seen on conventional imaging) was 4.1% (95% CI: 2.7%, 6.0%). TP: FP ratio was 0.92 (95% CI: 0.47, 1.82) and PPV 47.9% (95% CI: 31.8%, 64.6%.) Few studies included consecutive women and few ascertained outcomes in all subjects. Where reported, 35.1% of MRI-detected cancers were DCIS (mean size= 6.9mm), 64.9% were invasive cancers (mean size= 9.3mm), and the majority were stage pTis or pT1 and node-negative. Effect of pre-operative MRI on treatment was inconsistently and incompletely reported, however based on 11 studies reporting data in some or all cases, there was indication that mastectomy was performed frequently.

Conclusion

MRI detects (occult) contralateral early-stage disease in a substantial proportion of women with newly diagnosed invasive breast cancer, but does not reliably distinguish benign from malignant findings. Low summary PPV reinforces that surgery should not be based on MRI suspicion. Women must be informed of the uncertain benefit and potential harm including additional intervention. Surgical treatment attributed to MRI screening of the contralateral breast has been inadequately reported in most primary studies, and warrants further evaluation; mastectomy was frequently reported. The large proportion of DCIS amongst MRI-detected CBC raises the issue of whether detection of such lesions improves long-term outcomes in the context of current systemic therapy for ipsilateral invasive cancer which may prevent some contralateral cancers.

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Interval between breast-conserving surgery and radiotherapy in early-breast cancer: How long before an effect on local control?

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Background and purpose

To critically appraise the assertion that an interval beyond 8 weeks between breast-conserving surgery (BCS) and adjuvant radiotherapy (RT) in early-breast cancer increases the risk of local recurrence in the absence of chemotherapy.

Methods

A full review of the recent literature, including results of single and multiple institutional clinical databases, randomized clinical trials on sequencing of RT, administrative databases, and a critical appraisal of a main meta-analysis[1] on the topic were undertaken.

Results

The appraisal of one main meta-analysis on wait time and risk of local recurrence has highlighted significant short-comings and risks associated with the dual role of research and patients' advocacy, which can lead to misleading conclusions. Data of good quality does not demonstrate an increased risk of local recurrence if RT is started within 20 weeks of BCS.

Conclusions

An interval of up to 20 weeks between BCS and radiotherapy in early-stage breast cancer is not associated with an observable impact on local control. For years, intervals beyond 8 to 12 weeks were common in Canada, Australia, and UK. Long delays to treatment cause patients and families anxiety, in part due to concerns about cancer progression. It is recommended to start RT as soon as reasonably achievable following BCS. When there are delays the patient's anxiety should not be magnified by suggesting that there is evidence of cancer progression during intervals up to 4 months from BCS.

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Mastectomy and reconstruction: An increasing trend in the last 10 years

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Notes

Background and purpose

The aim of this study was to examine mastectomy rates and the indications for mastectomy over a 10 year period between 1998 and 2008 performed by our unit. We were particularly interested to know indications for mastectomies being performed. Over this time period prophylactic mastectomies in patients with high genetic risk factors have been proven to reduce the rate of breast cancer. We were keen to document the changing indications for mastectomy in our unit over the past decade.

Methods

The medical records of patients who underwent mastectomy and reconstruction in the years 1998 and 2008 treated in our department were retrospectively reviewed. A total of 101 patients (114 breasts) were involved.

Results

The number of breast cancers diagnosed by our unit increased from 87 to 112 (128%). The mastectomies performed in our unit increased significantly (chi square $p<0.01$) from 28 to 62 per annum (221%). The increased number of mastectomies can be attributed to increased diagnosis of multi-focal cancer (4 to 12), patient preference for prophylactic mastectomy and increased identification BRCA gene mutations (1 to 5). Prophylactic mastectomy as a result of patient preference has increased from 0 to 8 ($p=0.05$) and bilateral mastectomy has also increased from 0 to 16 ($p=0.002$). At the same time, the reconstruction rates have increased from 7 to 30 per annum (428%, $p<0.001$).

Conclusions

In our unit the increased mastectomy rates reflect more sophisticated pathological diagnosis as well as patient preference factors, particularly increased awareness of breast cancer risk and acceptance of prophylactic surgery in the management of BRCA/high risk patients. Improved access and changes in perception relating to reconstructive breast surgery also appears to have influenced patient choice.

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Core biopsy evaluation of papillary lesions of the breast

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Background and purpose

Asymptomatic papillary lesions diagnosed on core biopsy are generally excised to establish a definitive diagnosis. As the majority of papillary lesions are benign, an accurate core biopsy prediction of the final diagnosis may usefully guide further management. The aim of this study was to determine whether histopathologic features could consistently identify benign papillary lesions on core biopsy.

Methods

A cohort of 127 excised papillary lesions was characterised by detailed histopathologic review and immunohistochemical staining for CK 5/6, P63 and Ki67. Comparison of benign, atypical and malignant lesions formed the basis of a putative diagnostic classifier applicable to core biopsies. The classifier was tested in an independent series of 42 cases.

Results

Benign papillary lesions tended to show thick fibrovascular cores and a mosaic pattern of CK5/6 staining. Ki67 staining revealed striking intra-lesional heterogeneity but there was no difference between the high scores of benign, atypical or malignant lesions (p=0.5). A binary classifier specifying benign lesions on the basis of thick fibrovascular cores and any intra-lesional CK5/6 staining gave an overall misclassification rate of 4/42 (9.5%). This included 2/27 benign lesions (7.4%) designated as atypical/malignant and 2/2 atypical cases classified as benign. All malignant lesions (n=13) were accurately classified.

Conclusions

Combined assessment of fibrovascular core thickness and CK 5/6 staining can accurately distinguish benign and malignant papillary lesions on core biopsy. Atypical lesions remain difficult to identify, probably due to the combined effects of intra-lesional heterogeneity and limited sampling.

The breast cancer tissue bank

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Notes

Background and purpose

The Breast Cancer Tissue Bank (BCTB, www.abctb.org.au) project began in 2004 in response to widespread recognition that the availability of high quality biospecimens and data was vital to future progress in breast cancer research. The original aims of the project were 1) To establish a standardised framework for the ethical and appropriate collection of biospecimens and clinical follow-up data; 2) To collect tissue, blood and standardised clinical data from breast cancer patients; and 3) To make material available for basic and translational research.

Methods

The BCTB, based in NSW, has a 'hub and spoke' structure with a central management core at Westmead Hospital and six collection centres across the state. A key feature of collection centres is that activities of the BCTB are integrated into breast cancer treatment facilities. The central management core oversees resourcing, standard operating procedures, quality management and a web-based relational database.

Results

Over 2000 individuals have now been enrolled as donors to the BCTB and new donors are recruited at a rate of approximately 100 per month. Since the availability of materials was advertised in 2008, over 1500 biospecimens have been approved for provision to researchers. In 2007 the BCTB established a central specimen processing facility to maximise the efficient use of materials. This facility has capacity to perform automated DNA extraction from blood, DNA and RNA extraction from tissue, tissue microarray construction and section imaging.

Conclusions

The BCTB is now a fully functioning biospecimen and clinical data resource that is accessible to all Australian breast cancer researchers by application.

SESSION 4: PREVENTION, DETECTION AND PROGNOSTICATION

Notes

Keynote address: Are circulating cells an established prognostic factor?

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Recently, several technical advances have led to important studies that suggest that tests for circulating tumor cells (CTC) may gain a role in clinical care of patients with breast and other malignancies.

Technology to identify CTC

CTCs are a rare component among the billions of cells within the human bloodstream. To identify CTC, investigators have exploited differences between epithelial cells and normal hematopoeitic cells or between malignant and normal epithelial cells[1]. Two major strategies have been used to exploit these differences. In one, whole blood is subjected to density gradient centrifugation and/or erythrocyte lysis to separate nucleated cells from erythrocytes, and then the nucleated cell fraction is examined by a variety of means to identify the CTCs. For example, reverse transcription polymerase chain reaction (rt-PCR) has been used to detect transcription of genes, such as cytokeratin, that should normally not be present in blood[2]. In addition to cytokeratin transcripts, investigators have reported detection of CTC using rt-PCR against MUC-1, carcinoembryonic antigen, epithelial cell adhesion molecule (EPCAM), mammoglobin, HER-2, and other genes. A second strategy to separate epithelial cells from whole blood exploits immunomagnetic or other immuno-separation techniques. These cells are then further characterized with labeled probes, such as antibodies against other epithelial or putative tumor specific antigens. Recently, a fully automated immunomagnetic and immunofluorescent system for detection of CTCs has been developed (CellSearch™, Immunicon Inc, Huntingdon Valley, PA). This system utilizes microscopic ferro-fluids that have been coated with an antibody against EPCAM to magnetically separate epithelial cells from whole blood. The isolated cells are then characterized as CTC based on cellular size and morphology, staining with DAPI, staining with a fluorescently-labeled cocktail of pan anti-cytokeratin antibodies, and absence of staining for the leucocyte specific antigen, CD45. Other systems using immunomagnetic and immuno-characterization of CTC have been reported, but their development appears less mature than that for CellSearch™ in regards to specific clinical utility.

rt-PCR and immunomagnetic/fluorescent approaches have relative pros and cons. Broadly, although not without argument, the rt-PCR method appears to be the more sensitive and the immunomagnetic / fluorescent approach appears to be more specific. The latter may also provide the opportunity for further characterization of the cells. However, the two strategies have not been rigorously compared head-to-head in clinical trials. Indeed, they are not mutually exclusive, as some investigators have used an initial enrichment immuno-separation step followed by rt-PCR[3].

Recently, other innovative methods have been described to isolate CTC based on physical and biological differences between epithelial malignant and normal cells, for example, using micro-posts coated with anti-EPCAM antibody have been used to capture epithelial cells[4], or based on secretion of epithelial-associated or even tumor-associated soluble proteins using the so-called "Epi-spot" technology[5], or using a microfiltering coupled with electrolysis and rtPCR[6]. Preliminary reports of these assays suggest remarkable sensitivity and potential for further cellular characterization, but the specificity and clinical utility of these assays is undetermined.

Setting and possible utility of CTC

As with all tumor markers, CTC might be useful in one of several clinical situations in breast cancer, including risk determination, screening, differential diagnosis, determination of prognosis in either the adjuvant or metastatic settings, prediction of specific benefit from particular therapies, or monitoring patients who are either free of disease for occult recurrence or those who have established metastases to determine disease course. At this time, there is no indication that any assay for CTC has sufficient sensitivity or specificity to be useful as a risk or screening tool, or to distinguish malignant from benign lesions or one type of malignancy from another. However, there is a growing body of literature to suggest that CTC might provide useful clinical information either in newly diagnosed patients or in those being monitored for recurrence or during treatment of metastatic disease.

CTC in patients with operable, early-stage breast cancer

Studies have suggested that CTC can be found in up to 40% of patients with newly diagnosed breast cancer when assayed by rt-PCR and in approximately 10% using CellSearch™[1]. It appears that 20-30% of patients with stage I or II breast cancer have positive rt-PCR results for cytokeratin 19 transcripts and these patients have a poorer prognosis than those without CTC. The presence of CTCs appears to be associated with a poorer prognosis at diagnosis regardless of nodal status or whether patients receive adjuvant systemic therapy. Recent reports have suggested that rising CTC results during or residual CTCs after adjuvant may predict that the ongoing or prior therapy is ineffective. These provocative results are consistent with findings by other investigators regarding bone marrow micrometastases[7].

Presently it is not clear how one might use CTC levels to make clinical decisions in the adjuvant setting. Each of these studies has been conducted within patient cohorts in which therapy was not prospectively dictated, and no study has used CTC results to direct therapy in comparison to a group of patients treated using standard prognostic and predictive criteria. Given the overall survival benefit of adjuvant chemotherapy, use of a tumor marker, such as CTC, to make clinical decisions must be considered very carefully.

CTC in patients with metastatic breast cancer

While an occasional patient with metastatic breast cancer appears to be cured, most are destined to ultimately die of their disease. Thus, the goal of therapy for most patients with metastatic breast cancer is to choose the therapy with the highest likelihood of response and the lowest possibility of toxicity, thus balancing symptoms of the cancer with side effects of treatment. Once a palliative treatment regimen is selected for a patient with metastatic breast cancer, it is generally continued until either undue toxicity or evidence of progression. Current methods of determining progression include history, physical examination, serologic testing, and radiographic evaluation. The ASCO Tumor Marker Guideline Panel has recommended that assays for MUC-1 proteins (CA15-3, CA27.29) and for carcinoembryonic antigen (CEA) may be helpful in monitoring selected patients with metastatic breast cancer[8].

Elevated CTCs are found in 50-75% of patients with metastatic breast cancer using either rt-PCR or immunomagnetic/fluorescence approaches. In a prospective, multi-institutional clinical trial involving women with measurable, progressive metastatic disease who were about to start a new therapy, elevated CTC at any time point, using CellSearch™, were associated with a high likelihood of a very short time to progression[9-12]. In this trial, 50% of these patients had elevated CTC before starting a new treatment, and their prognosis was worse than those without elevated CTC. Importantly, at the first follow-up visit after starting a new therapy (usually 3-5 weeks), only 30% had elevated CTC levels. Patients with persistently elevated CTCs had a worse prognosis than patients who "cleared" their CTCs, and the latter patients had a favorable prognosis, similar to those women without CTC at baseline, suggesting a therapeutic response (Figure 1)[9,10]. Likewise, elevated CTCs at later time points were always associated with rapid subsequent progression[11]. Although the recently released ASCO Tumor Marker Guidelines did not recommend use of CTCs in metastatic disease[8], we believe it is reasonable to use CTCs to make clinical decisions after several months of therapy in patients with metastatic disease, especially those with non-measurable disease in whom classic clinical, serologic and radiographic findings are non-diagnostic.

Residual CTC at first follow-up is an indication of a very high likelihood of rapid progression[9]. It is possible that changing therapy at this time-point might be more beneficial than maintaining an apparently futile treatment regimen. Such a recommendation would establish a new and unfamiliar paradigm in the treatment of metastatic breast cancer. Therefore, a prospective randomized clinical trial addressing the value of immediate change in therapy vs. waiting until classic clinical and radiographic findings of progression is now being conducted within the North American Breast Cancer Intergroup, led by the Southwest Oncology Group (S0500).

In summary, technology to detect and characterize CTCs is advancing rapidly. We believe that early studies already suggest a role in selected patients with metastatic disease. We anticipate that, coupled with an increasing understanding of the need for well designed and conducted trials, better understanding of the biology of CTC will result in their becoming a routine part of the clinical evaluation of at least patients with metastatic breast and other cancers, and perhaps even in early stage disease.

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Role of genomics in predicting prognosis

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Breast cancer is the commonest malignancy in women. It is a heterogeneous disease with multiple sub-types, variable size, grade, metastatic potential and with varying prognosis. The examination of the standard H&E section is still an efficient, cost-effective and powerful mode of providing information to inform classification and hence prognosis and clinical management. None-the-less, the developments in our understanding of the molecular and cellular basis of cancer initiation and progression is providing tools for refining breast cancer taxonomy and is opening up new avenues for prognostication and the treatment of breast cancer.

The use of immunohistochemistry (IHC) for differentiating benign from in-situ and invasive malignancy using a variety of cell and tissue specific molecules such as cytokeratins and basement membrane markers has made significant impact on clinical management. Staining for oestrogen receptor (ER), Progesterone receptor (PgR) and Epidermal Growth Receptor II (HER2) is becoming standard practice and increasingly, gene amplification studies for HER2 have also been incorporated into the testing. These molecular tests already help us to stratify breast cancers into meaningful groups for prognostication and treatment.

Recently, a variety of microarray based technology, looking at the genomic profiles and expression of thousands of genes simultaneously has been used to sub-classify breast cancer and 'signatures' for prediction of 'good versus bad' and 'responsive versus non-responsive' cancers have been reported. There is little doubt that the methods have given us considerable insights into the biology of breast cancer and its heterogeneous nature. It is also clear that ER, HER2 and proliferation are central to many of the molecular signatures identified for classification as well as prognosis. Whether these molecular profiles add significantly to stratifying patients into meaningful groups above and beyond what can be done with simple morphology and immunophenotyping remains to be seen.

The emerging technologies do hold much promise for adding to and extending the current classification of breast cancer to help optimise patient management but much remains to be done in terms of standardisation of platforms, use of appropriate quality control, statistical methods for analysis and cut-offs used to separate cancers into different groups.

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Keynote address: Screening for high risk women

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Women can be at increased risk from breast cancer as a result of their family history. Those who are at a significantly raised risk should be assessed by a medical geneticist who can take a detailed history and assess their risk, and who can offer counselling as to appropriate management and offer breast screening [1]. Currently mammography with magnetic resonance imaging is considered the optimal method of early detection of breast cancer in these women. While there is no evidence of mortality benefit there is evidence from surrogate markers that this intervention is worthwhile and cost effective. National recommendations have been offered by a number of bodies including the National Institute of Clinical Excellence in the UK and the American Cancer Society.

Gene testing can be undertaken which can help refine the breast cancer risk estimate. Approximately 5-10% of breast cancer is caused by an inherited mutation. The best known are the tumour suppressor genes *BRCA1* and *BRCA2.*

In the UK women can be grouped into high, medium and low risk. High risk is defined as greater than 8% chance of developing breast cancer over the next 10 years; or a lifetime risk of more than 30%; or a greater than 20% risk of having faulty *BRCA1, BRCA2* or *TP53* gene in the family. Medium risk is 3-8% over 10 years; or a lifetime risk of 17-30%. This compares to a population risk of <3% chance of developing breast cancer over the next 10 years when aged 40-49. The lifetime risk to the population is under 17% [1].

The US preventive services task force analysis of the seven randomised trials of mammography screening has shown that a mortality reduction of 22% can be expected in the over 50 age group and 17% in the 40-49 age group [2]. The reduction in mortality is dependent on the size and node status of tumours that are detected, with a population screening programme expected to achieve an 80% node negative rate.

The national studies comparing Magnetic Resonance Imaging (MRI) with mammography have all shown that MRI has a much higher sensitivity for cancer detection than mammography (71-94% and 36-59% respectively). The specificity for screening MRI was lower than with mammography. The Canadian study was a single centre trial of 236 women aged 25-65 who were known gene carriers, of whom 70 had had previous breast cancer [4]. The Dutch study recruited 1,909 unaffected women aged 25-70 years who were estimated to have at least a 15% lifetime risk of developing breast cancer at six centres. 19 were known gene carriers [4]. The UK MARIBS trial reported 649 unaffected women aged 35-49 years who were gene carriers or at greater than or equal to 50% risk of having a gene from 22 centres [5]. The German single centre study screened 529 women over 30 years who were at least 20% lifetime risk from their family history or their personal history of a previous breast cancer [6]. The five centre Norwegian study of 445 *BRCA1* and 46 *BRCA2* gene carriers examined the added benefit of MRI to annual mammography [7]. The nine centre Italian study reported 278 women aged 25 years or older with a risk of greater than 25% [8].

Ductal carcinoma in situ (DCIS) can be difficult to detect with MRI particularly where the voxel size of the MR images is large. Combining data from the published studies showed there were 35 cases of DCIS. This was detected with a sensitivity of 53% by MRI and 57% by mammography. However in a single site study a much higher sensitivity was found using a high resolution technique [11].

The trials of annual screening in the high risk cohorts that included breast ultrasound showed disappointing results for this technique. The sensitivity ranged from 33-40% in the earlier studies [3,6] but improved to 65% in the mostly recently published Italian study [8]. However it may be that the combination of US with mammography will give results comparable to MRI. In the Norwegian high risk screening study US is used in addition to mammography and MRI in women with dense breasts [7]. Berg reported a large multicentre study of screening US and mammography in women at increased risk [10]. The average age was 55 years and 2637 women were analysed. Using standardised scanning and interpretive criteria this study showed a diagnostic accuracy for US of 80% compared to mammography of 78% and a combined accuracy of 91% (p=0.003). The number of false positives is considerably higher than with mammography. The authors concede that where screening MRI is performed US is not necessary except in the workup of abnormalities identified by MRI.

There is little support for using formal breast examination as a screening tool. There is no evidence of benefit in a screening setting. In the four trials of high risk women where CBE has been reported the sensitivity varied between 5-50% [3, 4, 6, 8] with high specificity. The Italian study showed the highest cancer detection although the reason for this is not clear. The Norwegians abandoned CBE by national consensus between the oncologists, surgeons and geneticists [7].

Although there is good evidence that MRI has greater sensitivity than mammography for detecting cancer and also for a stage shift to a more favourable prognosis, there is no direct evidence that this translates to a mortality benefit. It is highly unlikely that a randomised trial

comparing MRI and mammography screening with mortality endpoint will be undertaken so surrogate markers are used to impute benefit. However this is subject to lead time bias. Data from the trials suggest that 74-94% of tumours are <2cm in size, 11-27% are DCIS and 76-87% are node negative. The Dutch did a direct comparison with age matched historical controls and showed that the proportion of tumours <1cm in size was significantly greater in the surveillance study (43.2 %) than in either of their control groups (14% and 12.5%) and similarly showed that the node positive rate of 21.4% was significantly better than the controls (52.4% and 56.4%) [5]. However Hagen compared the combined MRI and mammography to the previous mammography only protocol in the *BRCA1* carriers and showed very similar DCIS rates and node negative rates (16%, 8% and 26%, 27% respectively) but fewer pT2 tumours detected by MRI compared to previous mammography alone [7]. These surrogate endpoints suggest that there may be a mortality benefit similar to that achieved by mammography in the population randomised screening trials. However many tumours in this high risk group are of basal phenotype and grade 3 suggesting that a poorer survival should be expected. Important information will be gained from collecting recurrence and survival data from these screened cohorts.

Guidelines for screening high risk women

The UK NICE guidelines on familial breast cancer recommend annual MRI is offered with mammography to all gene carriers and those at 50% risk of being a gene carrier from age 30 years. This should be done in conjunction with mammography unless the woman is a p53 carrier where there is concern of increased sensitivity to radiation damage. The MRI screening programme will be run under the auspices of the National Health Breast Screening programme and will be quality controlled through this organisation. Guidelines on the MRI protocols and reporting standards will be issued by the breast screening programme and will follow recommendations from the Royal College of Radiologists Breast Group.

The American Cancer Society breast cancer advisory group has issued guidelines for breast screening with MRI as an adjunct to mammography [12]. Women with more than a 20-25% lifetime risk of developing breast cancer as a result of their family history or previous mantle radiotherapy between age 10-30 years for Hodgkin's disease should be offered annual MRI. Women at less than 15% risk should not be offered screening. It is suggested that screening begin at age 30 years although this is not evidence based.

There is now considerable evidence that the addition of MRI to mammography screening in high risk women will improve stage of cancer detection. Further information is required to ascertain whether this is conferring a mortality benefit for these women. National guidelines should be followed, the quality of the service audited to ensure highest standards of MRI are adopted and follow up information on cancer detection and survival gathered.

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Keynote address: The use of prophylactic surgery in high risk women

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Assessing the risk of developing breast cancer aids both the patient and the clinician in developing a comprehensive screening and prevention strategy. It is important to determine epidemiologic events, risk of genetic mutations, such as deleterious mutations in the BRCA1 or 2 genes, and potential for other hereditary breast cancer syndromes. Additionally, a woman who has been diagnosed and treated for breast cancer has an increased risk of developing a new cancer in the contralateral breast in her lifetime. Once breast cancer risk is assessed, a woman may have multiple options including surveillance with clinical breast exams, mammography and MRI, chemoprevention strategies or prophylactic surgery. This review will discuss risk assessment and counseling for screening and preventative modalities.

Risk assessment tools

Risk factors for development of breast cancer include gender, age, endocrine factors, benign high risk breast lesions, dietary and lifestyle factors, a personal history of breast cancer and a family history of breast cancer. Increased exposure to estrogen has been associated with developing breast cancer and factors that increase the number of menstrual cycles, such as early menarche, nulliparity, and late menopause, are associated with increased risk. Obesity is associated with a long-term increase in estrogen exposure and increased breast cancer risk. Additional risk factors include radiation exposure, alcohol consumption and a high fat diet. The average lifetime risk of breast cancer for women in the U.S. is 12%. The most common risk assessment tool is the Gail model, which incorporates age at menarche, the number of breast biopsies, age at first live birth, and the number of first-degree relatives with breast cancer. This model predicts the cumulative risk of breast cancer according to decade of life. A software program is available from the National Cancer Institute incorporating the Gail model (http://bcra.nci.nih.gov/brc). This model was also recently modified to assess risk in African American women. A second risk assessment model is that developed by Claus and colleagues, which is based on assumptions about the prevalence of high-penetrance breast cancer susceptibility genes. The Claus model incorporates more information about family history, but excludes other known risk factors.

None of these models account for the risk associated with mutations in the breast cancer susceptibility genes BRCA1 and BRCA2. Factors that increase the likelihood of an individual harboring a BRCA mutation include a family history of multiple cases of early onset breast cancer, ovarian cancer with a family history of breast or ovarian cancer at any age, breast and ovarian cancer in the same woman, bilateral breast cancer, Ashkenazi Jewish heritage, and a family history of male breast cancer. Appropriate counseling for the individual being considered for genetic testing is strongly recommended. In a family with a history that is suggestive of hereditary breast cancer but without a previously tested member, the most informative strategy is to test an affected family member first. If a mutation is identified, other relatives are usually only tested for that specific mutation. A positive test is one that reveals the presence of a BRCA mutation that interferes with translation or function of the BRCA protein. An individual who carries a deleterious mutation has a breast cancer risk of up to 85%, as well as a significantly increased risk of ovarian cancer. A negative test result is interpreted along with an individual's personal and family history.

Other hereditary syndromes associated with an increased risk of developing breast cancer include Cowden's syndrome (PTEN mutations), Li-Fraumeni syndrome (p53 mutations), syndromes of breast-melanoma.

Risk management strategies

Current risk management strategies for high risk women include, clinical and radiologic screening, chemoprevention, prophylactic mastectomy and prophylactic oophorectomy.

Current screening recommendations for BRCA mutation carriers who do not undergo prophylactic mastectomy include clinical breast exam every 6 months and mammographic screening every 12 months, beginning at age 25 years. Recent attention has been focused on the use of magnetic resonance imaging (MRI) for breast cancer screening in high-risk individuals and known BRCA mutation carriers. The current recommendations from the American Cancer Society are for annual MRI in women with a 20% to 25% or greater lifetime risk of developing breast cancer, including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin's disease in their teens or early twenties.

Tamoxifen, a selective estrogen receptor modulator, was the first drug shown to reduce the incidence of breast cancer in healthy women. The National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial randomly assigned over 13,000 women, with a 5-year Gail relative

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risk of breast cancer of >1.69, to tamoxifen or placebo. Tamoxifen reduced the incidence of breast cancer by 49% and is currently approved for breast cancer risk reduction. Tamoxifen is associated with risk of deep venous thrombosis, pulmonary emboli, endometrial cancer and increased risk for cataract formation. There is a model developed by Gail and colleagues that accounts for medical co-morbidities in order to determine the net risk-benefit ratio of tamoxifen use for chemoprevention. The second NSABP chemoprevention trial (P-2), compared tamoxifen and raloxifene for breast cancer risk reduction in high risk postmenopausal women. Raloxifene, another selective estrogen receptor modulator, has been used for managing osteoporosis in postmenopausal women. The P-2 trial randomized 19,000 postmenopausal women at high-risk for breast cancer and found that the two agents were similar in their ability to reduce breast cancer risk, but raloxifene had a more favorable adverse risk profile. Both agents reduced the risk of developing breast cancer by about 50% but tamoxifen also reduced the incidence of lobular carcinoma *in situ* (LCIS) and ductal carcinoma *in situ* (DCIS). The P-1 and P-2 trials assessed chemoprevention in high-risk women but did not routinely test for BRCA mutations. The available data regarding chemoprevention with tamoxifen or raloxifene is limited and it is therefore difficult to recommend the use of tamoxifen uniformly for BRCA mutation carriers. Most studies have demonstrated that breast cancers arising in BRCA1 mutation carriers are most often hormone receptor–negative. Approximately 66% of DCIS lesions in BRCA1 mutation carriers are estrogen receptor–negative, suggesting early acquisition of the hormone-independent phenotype. Since tamoxifen appears to be more effective at preventing estrogen receptor-positive breast cancers, this may not be the most effective strategy for BRCA mutation carriers.

Multiple studies have shown that bilateral prophylactic mastectomy can significantly reduce the incidence of breast cancer in high risk women. Hartmann et al. reported on a retrospective study of women at high risk for breast cancer and found that prophylactic mastectomy reduced their risk by more than 90%. The PROSE study group evaluated 289 BRCA mutation carriers, 105 of which had prophylactic mastectomy, and only 2 (1.9%) developed a subsequent breast cancer. This study estimated a 95% risk reduction from prophylactic mastectomy in BRCA mutation carriers. Another study involving women who were carriers of a BRCA mutation found that the benefit of prophylactic mastectomy differed substantially based on the breast cancer risk conferred by the type of mutation. In women with an estimated lifetime breast cancer risk of 40%, prophylactic mastectomy added approximately 3 years of life, whereas in those women with an estimated lifetime risk of 85%, prophylactic mastectomy added more than 5 years of life.

The use of contralateral prophylactic mastectomy in breast cancer patients without BRCA mutations, has not been shown to have an impact on survival. Despite this information, several investigators have reported an increasing trend in contralateral prophylactic mastectomy in the United States. Investigators at the Mayo Clinic, used questionnaires to understand treatment decisions in women undergoing contralateral prophylactic mastectomy and reported that the majority of women (83%) were satisfied with their decision.

The use of skin-sparing mastectomy has improved cosmetic outcomes and has local-regional recurrence rates similar to standard mastectomy in early-stage breast cancer patients. A further advance is the preservation of the nipple-areolar complex as part of the skin-sparing mastectomy. The safety of this approach has been reported by several investigators, however, each series is small in number and follow-up times are short.

Surgical bilateral salpingo-oophorectomy (BSO) has been used as a breast cancer prevention technique as well as to decrease the risk of ovarian cancers in women with known BRCA mutations. It has been estimated that BSO performed in premenopausal women may decrease breast cancer risk 50%. Domchek and colleagues have reported that BSO results in improved overall and disease-specific survival in BRCA mutation carriers. The American College of Obstetrics and Gynecology recommends that women with documented BRCA mutations should consider prophylactic oophorectomy at completion of childbearing or at menopause. Hormone replacement therapy is not routinely recommended but can be discussed with the patient at the time of oophorectomy. Yearly transvaginal ultrasound and annual serum CA 125 levels beginning at age 25 are the screening modalities for ovarian carcinoma in BRCA mutation carriers who defer prophylactic oophorectomy.

Conclusions

It is important to assess each individual's risk of developing breast cancer prior to determining the appropriate management strategy. In women with a known genetic predisposition to breast cancer, the addition of breast MRI should be considered in addition to the standard guidelines for breast cancer surveillance. Current chemoprevention strategies include tamoxifen in both premenopausal and postmenopausal women and raloxifene in postmenopausal women. The use of these agents in BRCA mutation carriers is less well studied. The use of prophylactic mastectomy is associated with a 90% risk reduction in high risk individuals and may be improve survival in BRCA mutation carriers. Prophylactic oophorectomy is a strategy for breast cancer and ovarian cancer risk reduction. There is no evidence that contralateral prophylactic mastectomy improves survival in women with a breast cancer diagnosis.

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SESSION 5: THE MANAGEMENT OF METASTATIC DISEASE

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Pathologic predictors of locoregional and distant metastasis: Part 1

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Breast conserving treatment (BCT) has been proven to be equivalent to mastectomy in overall survival. Breast conservation is appropriate for early stage breast cancer, including ductal carcinoma in situ (DCIS) and, thanks to the advent of neoadjuvant chemotherapy, many examples of large primary breast carcinomas may ultimately be treated conservatively. Despite careful patient selection, occasionally breast carcinoma recurs locally. In addition to significant anxiety, this treatment failure often requires mastectomy, negating the original intent of breast conservation. It is important to distinguish local recurrence linked to increased risk for distant spread from the local recurrence due to inadequate local treatment. This difference is not always evident, making comparison of different series difficult because of the lack of uniform treatment.

Studies have focused on identifying pathologic and clinical characteristics that predict for locoregional as well as distant recurrence. Characteristics of the primary breast carcinoma, and especially factors that reflect the adequacy of the initial surgery, correlate with the likelihood of local recurrence. True local recurrence may come from residual malignant cells present in peritumoral tissue, peritumoral lymphatic spaces, or foci of DCIS beyond the primary tumor. From these sites, it is logical to assume that the following prognostic factors, peritumoral lymphovascular invasion (PTLVI) extensive intraductal component, and positive resection margins may predict disease recurrence. Interestingly, PTLVI predicts both local and distant recurrence, while an extensive DCIS component predicts only for local relapse.[1] Obtaining wide surgical margins appears to be the strongest prognostic factor for local recurrence, regardless of other pathologic factors or the addition of adjuvant radiation therapy.[2]

In most series, predictors of distant recurrence include tumor size and axillary lymph node involvement. These factors do not predict for local recurrence however. Understanding the predictive ability of factors associated with local recurrence is complicated by the competing risk of distant recurrence. In a well-characterized breast conservation cohort, young age, peritumoral lymphatic invasion, and an extensive intraductal component were risk factors for local recurrence. Young age and peritumoral lymphatic invasion also predicted for distant recurrence. This study also provides good evidence that local recurrence and distant metastases are partially interdependent events.[1]

A local recurrence may imply either incomplete removal of tumor or it may equate to tumor aggressiveness. The former argument is supported by studies that show lesser surgical approaches may result in enhanced rate of local recurrence. On the other hand, the idea that local recurrence is the result of tumor aggressiveness is supported by the fact that women who have a local recurrence are at three-times increased risk for developing distant metastasis. If local recurrence equates to tumor aggressiveness, then local recurrence and distant metastatic potential should be associated with the same prognostic markers, which is only partially the case [1]. In fact, both hypotheses are likely to be partially true.

The relationship between local and distant recurrence is complex. The timing of local recurrence and distant metastasis differ. The yearly probability for local recurrence is 1% each year for the first 10 years, and for distant metastasis, 5% in the 2nd year, decreasing until the 8th year.[1] The earlier a local recurrence appears, the higher the risk of distant metastasis.[1] If local recurrence is linked to distant spread, opportunities exist to initiate aggressive systemic therapy. When local recurrence is linked to inadequate initial local therapy, local management may be instituted.

Factors that do not have an impact on local regional recurrence include the resection volume[3] or the need for multiple re-excisions[4]. Also histologic subtype (that is recognition of special type carcinomas) does not protect against local recurrence, as shown by Thurman et al. They compared the local recurrence rate of 20 patients with either Stage 1 or Stage 2 mucinous, medullary, and tubular carcinoma with the recurrence rate of more than 1000 patients with invasive carcinoma of no special time. Factors associated with local failure included young age, positive surgical margins, lymphovascular invasion, and tumors with an extensive intraductal component. Regional, distant, or opposite breast failure was associated with Stage 2 tumors, those patients with 4 or more positive lymph nodes, and lymphovascular invasive carcinomas.[5]

Histologic type of breast carcinoma does not preclude breast conservation. Conservative surgery and radiation therapy is equally effective for invasive lobular carcinoma as it is for carcinomas of

no special type (invasive ductal carcinoma).[6] The role of lobular carcinoma *in situ* as a predictor of risk of recurrence has been evaluated by Abner, et al.[7] The presence of LCIS within the excision specimen did not have an impact on the risk of recurrence. Furthermore, having LCIS at a margin does not affect local recurrence.[8]

Much of the emphasis of local regional recurrence has focused on breast conservation approaches. Buchanan, et al. have presented data regarding the risk of loco- regional recurrence after mastectomy. Almost three percent of women developed a local regional recurrence and remained free of distant disease during the study. Factors associated with isolated local regional recurrence included young age (younger than 35), lymphovascular invasion, and multicentricity.[9]

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Is metastatic breast cancer curable?

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Obviously the answer to this question should be "No," or if one is feeling particularly generous, "No, not yet." Adenocarcinomas develop many years before they are clinically detectable, by which time they have become genetically homogeneous and unstable. Once apparent in metastatic sites, they have by definition developed the ability to intravasate, circulate, extravasate and prosper elsewhere, and they have done so in their billions. It seems intrinsically unlikely that such a situation could be reversed or that every last cell could be eradicated, and to date such is overwhelmingly our clinical experience.

And yet.

Treatment is now changing the natural history of breast cancer. As systemic adjuvant therapies become more effective we see fewer recurrences, and such recurrences that do occur may not do so for many years. It may not be completely unreasonable to expect that an oligo-metastatic presentation might give us a second opportunity at disease eradication. This is still likely to apply to only a small subset of patients and is unlikely to become a tractable question for a clinical trial. Thus the approach outlined below is primarily influenced by clinical anecdote and should remain highly contested:

(1) develop by multidisciplinary consensus a definition of candidates for "Maximum Disease Reduction" (MDR), for example:

> 3 or fewer surgically accessible sites of disease
>
> ECOG 0 or 1
>
> Disease-free interval > 5 years
>
> Enthusiastic

(2) review in multidisciplinary clinic the local therapy options (eg risks/feasibility of surgery versus radical radiotherapy versus other options such as SIRT)

(3) plan systemic therapy options (chemotherapy, endocrine therapy, targeted) and timing (before, during, after)

On the latter point, a case could be made for a period (say 3 months) of initial systemic therapy prior to definitive local therapy to the site or sites of metastatic sites. This would allow the clinician to gauge tumour sensitivity to the therapy and also give the tumour an opportunity to "declare" itself – if further disease were to become apparent so quickly after the initial diagnosis of metastatic disease, it is very unlikely that physical removal of the first sites of disease would have prevented development of the second. Thus major procedures could be avoided.

I would welcome discussion about this proposal.

Breast surgery in the context of metastatic disease

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Up to 10% of women presenting with newly diagnosed breast cancer will already have detectable metastases at distant sites (stage IV disease). Stage IV breast cancer has been considered an incurable disease with systemic treatment as the primary therapy and surgery reserved for palliation of symptoms. There have been numerous reports in other cancer types (colorectal, renal cell carcinoma, gastric and ovarian cancer) suggesting that aggressive local therapy improves overall survival. Significant improvements have been realized in the last decade in both the systemic treatment options and the survival outcomes for breast cancer patients leading to an interest in the surgical management of both primary and metastatic tumors in patients with stage IV disease.

Surgical resection of local-regional disease in women with stage IV breast cancer has become a point of debate after several reports have suggested that women who undergo resection of the primary disease have improved survival over those who do not. Khan and colleagues used the National Cancer Data Base to report on treatment patterns in women with metastatic breast cancer. They found that patients who had surgical resection of the primary tumor with negative margins had an improved prognosis over those women who did not undergo surgery. Gnerlich et al. used the SEER database and reported similar findings. There have been several retrospective series from single institutions that have also confirmed these findings. Some have suggested that there is selection bias accounting for the improved survival and that local and regional therapies should be reserved for palliation of symptoms. There are no randomized trials specifically addressing this issue with the exception of a Turkish trial that initiated accrual in October of 2007. That trial is planned to accrue 271 patients that will be randomized between surgery and no surgery for treatment of the local-regional disease in patients presenting with stage IV breast cancer. It seems unlikely that this trial will ultimately answer the question of the appropriate use of surgery in patients with metastatic disease with such a small sample size. In the absence of randomized data, we can use information from the available single institution trials in order to glean appropriate selection criteria for the stage IV breast cancer patient population that may benefit from surgical intervention.

The original report by Khan et al. from the National Cancer Database described a population of 16,023 patients with stage IV disease treated between 1990 and 1993. Of these patients, 43% did not have surgery or underwent only a palliative procedure, while 57% underwent either a partial or total mastectomy. Women who had surgery with negative margins had improved survival compared with patients who did not undergo surgery (HR of 0.61, 95% CI 0.58 – 0.65). On multivariate analysis, the number of metastatic deposits, the type of metastatic disease, and the extent of surgical resection were independent prognostic variables.

Shortly after the report from the National Cancer Database, Carmichael et al. reported on a small study from Edinburgh of 20 patients with stage IV disease at presentation or with evidence of metastasis within one month of their surgery. Median survival was 23 months with half of the patients alive without local recurrence at 20 months of mean follow-up time. Definitive conclusions could not be drawn since this was a small study and there was no control or comparison group.

A retrospective study from the MD Anderson Cancer Center was reported by Babiera and colleagues in 2006. This study included all stage IV patients who had an intact primary tumor treated between 1997 and 2002. Of the 224 patients treated in this timeframe, 37% underwent surgery while 63% were managed with systemic therapy alone.The patients who underwent surgery were younger, had less nodal involvement, had fewer sites of metastatic disease, more commonly had liver metastases, and more frequently had HER2-positive disease. At a median follow-up time of 32.1 months, there was an improvement in metastatic progression free survival and a trend toward improvement in overall survival in patients who had surgical resection of the primary tumor. Multivariate analysis demonstrated that only estrogen receptor positive tumors and patients who underwent surgical resection were associated with improved metastatic progression free survival. Multivariate analysis for factors impacting overall survival showed that patients with only one site of metastasis and those with lack of HER2 gene amplification had improved overall survival. There was a trend toward improvement in overall survival in patients who had resection of the primary tumor. In a follow-up study, Rao et al. showed that surgical resection of the breast tumor and axillary nodes greater than 3 months from diagnosis was associated with improved outcomes. This was particularly true in patients with negative margins and only one site of metastatic disease.

Rapiti and colleagues reported a population based observational study examining the outcomes of 300 patients from the Geneva Cancer Registry treated from 1977 to 1996. They found that patients who had complete resection of the primary tumor with negative margins had a 40% reduction in the risk of death from breast cancer compared with patients who did not undergo surgery. Patients who had surgical resection with positive margins had similar outcomes to

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those patients who did not undergo surgery at all. When examining for type of metastatic disease, the investigators noted that patients with bone only disease fared better with surgical resection.

Most recently, Cady and colleagues performed a case-matched comparison of stage IV breast cancer who did and did not undergo primary tumor resection from the breast cancer databases of two large institutions in Massachusetts. Of 19,464 patients treated between 1970 and 2002, there were 808 with stage IV disease. The initial survival analysis demonstrated an improvement in survival for patients who underwent surgical resection versus those who did not. The authors then case-matched patients with bone or visceral metastases and there was no longer an improvement in survival for patients who had surgical removal of the primary tumor. When the authors examined the sequencing of treatments (surgery and chemotherapy vs. chemotherapy alone) they found a similar phenomenon to that reported by Rao and colleagues, namely that patients who underwent delayed surgery after a period of chemotherapy had improved outcomes. They attributed this to selection bias since patients who responded to the systemic therapy were more likely to undergo surgery than patients who progressed on therapy.

Conclusions

There is a lack of randomized and prospective date on the role of resection of the primary tumor in patients who present with metastatic disease. While randomized trials are needed, they are unlikely to provide any evidence in the near future that will adequately address the clinical questions. In the meantime, surgical management of patients with stage IV disease should be addressed with multidisciplinary input and by considering the treatment goals of each individual patient and their treating physicians.

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Targeted treatments for metastatic disease

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Notes

Metastatic breast cancer is rarely, if ever curable[1]. Evidence is quite strong that survival after diagnosis has been prolonged over the last several decades due to application of systemic therapies[2]. However, in general, treatment of metastatic breast cancer is directed towards palliation, using prognostic and predictive factors, as well as psycho-social considerations, to keep patients feeling as good as they can for as long as they can. This approach requires a strategy of selecting the therapies most likely to work with the fewest side effects, and applying them sequentially. Indeed, I often tell patients that "the bad news is that you have metastatic breast cancer (and hence it is likely you will not be cured), but the good news is that you have metastatic breast cancer (because there are so many treatment options).

The first goal of therapeutic decision-making for metastatic disease is to determine if the patient has either a local problem requiring immediate action, such as surgery and/or radiation. This circumstance is most common with long-bone involvement and impending fracture, spinal cord compression with neurologic dysfunction, or symptomatic CNS metastases. Randomized clinical trials have demonstrated that the latter are best treated by surgery and radiation, rather than radiation alone, in regards to long term function return and even survival[3,4].

The second goal is to determine if the patient has rapidly progressive visceral disease, especially with end-organ dysfunction. If so, more immediate but toxic therapy, such as combination chemotherapy, might be indicated, since one may not have a chance to apply sequential therapies empirically.

Finally, assuming none of these conditions pertain (and they often do not), one should then evaluate predictive factors to determine if targeted therapies, which are usually quite active and have less toxicity than standard chemotherapy. The paradigm of targeted therapy for all cancer is the use of estrogen receptor (ER) to predict the benefit of anti-estrogen therapy[5]. There are many such therapies, and they can be used sequentially. There is little data to support combination endocrine therapy, which is admittedly more effective in inducing responses but does not appear to improve survival or cure rates, and does add toxicity. Endocrine therapy should not be used with chemotherapy, since this approach only adds toxicity, and in fact may result in antagonistic effects.

HER2 is amplified and/or over-expressed in up to 20% of breast cancers, and serves as the direct target of trastuzumab, a humanized mono-clonal antibody, and lapatinib, a small molecular weight tyrosine kinase inhibitor (TKIs). When added to chemotherapy, trastuzumab increases response rates, prolongs time to progression, and even lengthens survival when compared to chemotherapy alone[6]. Trastuzumab also is active when used as single agent therapy. Lapatinib is also active as a single agent, and patients with HER2 positive cancers who are refractory to trastuzumab have a reasonable chance of benefiting from lapatinib when combined with chemotherapy or, surprisingly, even with trastuzumab itself[7,8]. New agents that target HER2 are now under investigation, including pertuzumab, an antibody that targets a different domain of HER2, and DM-1, a trastuzumab-maytansine conjugate, as well as newer TKIs.

The concept of anti-angiogenesis has been widely studied, based on the long-proposed hypotheses of the late Judah Folkman. Bevacizumab, a humanized antibody directed against vascular endothelial growth factor (VEGF), has minimal activity in patients with heavily treated metastatic breast cancer, but appears to increase response rates and time to progression when applied in the first line setting[9]. Other putative anti-angiogenic agents, such as sunitinib and sorafenib, are under investigation.

Inhibitors of the AKT/MTOR pathway are now under study, but so far results have been disappointing. Just recently, exciting results suggesting that agents that inhibit poly XXX (PARP) have been reported. These small molecular weight orally active agents were developed principally to treat patients with so-called "triple negative" breast cancer (ER, PgR, and HER2). None is available commercially, but phase I single agent and randomized phase II data of chemotherapy plus PARPi vs. chemotherapy alone are quite encouraging[10]. None of these agents is yet available commercially, and definitive, phase III trials are opening soon.

Brain metastases remains a particularly problematic problem. Indeed, increasing evidence demonstrates that HER2 expression predisposes breast cancer to spread to the brain, and that isolated or earlier brain metastases are now being observed as systemic metastases in patients with HER2 positivity are controlled with trastuzumab, which does not cross the blood brain barrier. Early reports suggested that lapatinib crosses the BBB and might be an effective treatment for progressive brain metastases or even prevent them, but the available evidence in larger, more definitive studies has been disappointing[8,11]. Likewise, there is no evidence that bevacizumab is effective treatment for brain metastases, although it does appear to have activity in patients with primary brain cancers.

Notes

Newer targets are almost certain to be discovered either by gene candidate or multi-genetic expression analyses. These studies are expected to lead to even more options for patients with metastatic breast cancer, and perhaps even change the "uncurable" paradigm.

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Interventional radiology therapy for breast cancer metastatic to liver

Notes

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Metastatic breast cancer is best thought of as a systemic disease and treatment options should address metastases that may be present in bone, liver, lung, lymph nodes etc. However, there are some patients who present with either liver predominant disease or rapidly progressive liver disease in the setting of quiescent/responsive disease at other sites. These patients may die from the liver disease and loco-regional treatment may offer some benefit.

External beam radiotherapy is dose limited by toxicity to the normal hepatocytes and cannot be used as a whole liver treatment in tumoricidal dose. There is a long history of infusional therapy via the hepatic artery as treatment for metastatic liver disease especially in colorectal cancer with initial treatments using 5-flurouracil. It is known by the acronym TACE (Trans Arterial Chemo-Embolisation) and the rationale for this treatment is the almost exclusive hepatic arterial supply to growing metastases compared with the predominantly portal venous supply of unaffected liver. It is a whole liver treatment so disease location and volume are relatively unimportant providing the arterial anatomy can be accessed and understood.

Recently, particulate embolisation therapies have been developed and these take two forms:

Precision TACE uses a proprietary sphere (DC Beads, Biocompatibles) which can be loaded with a chemotherapeutic agent (doxorubicin or irinotecan). The beads are delivered at angiography into the hepatic artery and stick at capillary level (100- 300 micron size). The drug slowly leaches from the surface of the bead into the parenchyma/tumour providing active treatment over a 28 day period with much lower peak systemic drug levels and toxicity. Treatment cycle can be tailored to response but is usually about 6-8 weeks. Other systemic treatment is not precluded.

Radioembolisation uses an Yttrium labelled resin (SIRsphere) or glass (Therasphere) bead. The number of particles is lower so this is not a fill to stasis treatment and the Yttrium is a short radius beta particle emitter producing local tumoricidal effect with again a whole liver treatment intended.

Jakobs 2008: Sirsphere

30 patients with breast cancer metastases in liver. All heavily pretreated with anthracyclines, taxanes, hormonal Rx and some with traztuzumab.

23 patients follow up data at 5 months. Recist criteria 61%, 35%, 4% for PR, Stable and progressive disease. Mean survival time of responders 23.6 months, non responders 5.7 months.

Coldwell 2007: Sirsphere

44 patients with breast cancer metastases in liver. No treatment related deaths.

Recist PR on CT 47%; PET response 95% (>25% in PET activity (SUV))

Treatment given as a day patient / overnight stay following a work up session two weeks earlier which involves day case angiography, CT hepatic arteriogram and MAA Tc study to evaluate potential for transhepatic shunt of spheres and subsequent lung irradiation. Work up aims to understand hepatic and visceral arterial anatomy and avoid non target embolisation which is the cause of side effects and morbidity.

Current cost of Sirspheres treatment for uninsured patient at our centre is approx A$15,000 of which $9,500 is the cost of the treatment dose and $1200 are the hospital stay costs. Dose is currently reimbursed by health funds for Medicare 35404-6 which includes colorectal metastasis to liver in the item descriptor. Breast cancer metastasis does not qualify.

DC beads costs are reimbursible by health funds as are the costs of the attached drug and labelling.

Individual liver lesions can be targeted by radiofrequency ablation, cryotherapy, irreversible electroporation (IRE) or even surgery; however these are not whole liver treatments and may involve considerable collateral damage to normal liver eg partial hepatectomy. Metastatic breast cancer is seldom suitable for these therapies as more numerous and small volume disease is generally seen requiring a whole of liver treatment.

Palliative treatment:

Splanchnic nerve blocks: Rapidly enlarging liver metastases produce pain by capsular stretching or local irritation of the capsule. CT guided neuronolysis with 10% phenol is an outpatient procedure that can produce immediate and long lived reduction in pain for 4-6 months. It is well tolerated and highly effective and can be repeated if necessary.

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Pathologic predictors of locoregional and distant metastasis: Part 2

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Notes

Breast conserving treatment (BCT) has been proven to be equivalent to mastectomy in overall survival. Breast conservation is appropriate for early stage breast cancer, including ductal carcinoma in situ (DCIS) and, thanks to the advent of neoadjuvant chemotherapy, many examples of large primary breast carcinomas may ultimately be treated conservatively. Despite careful patient selection, occasionally breast carcinoma recurs locally. In addition to significant anxiety, this treatment failure often requires mastectomy, negating the original intent of breast conservation. It is important to distinguish local recurrence linked to increased risk for distant spread from the local recurrence due to inadequate local treatment. This difference is not always evident, making comparison of different series difficult because of the lack of uniform treatment.

Studies have focused on identifying pathologic and clinical characteristics that predict for locoregional as well as distant recurrence. Characteristics of the primary breast carcinoma, and especially factors that reflect the adequacy of the initial surgery, correlate with the likelihood of local recurrence. True local recurrence may come from residual malignant cells present in peritumoral tissue, peritumoral lymphatic spaces, or foci of DCIS beyond the primary tumor. From these sites, it is logical to assume that the following prognostic factors, peritumoral lymphovascular invasion (PTLVI) extensive intraductal component, and positive resection margins may predict disease recurrence. Interestingly, PTLVI predicts both local and distant recurrence, while an extensive DCIS component predicts only for local relapse.[1] Obtaining wide surgical margins appears to be the strongest prognostic factor for local recurrence, regardless of other pathologic factors or the addition of adjuvant radiation therapy.[2]

In most series, predictors of distant recurrence include tumor size and axillary lymph node involvement. These factors do not predict for local recurrence however. Understanding the predictive ability of factors associated with local recurrence is complicated by the competing risk of distant recurrence. In a well-characterized breast conservation cohort, young age, peritumoral lymphatic invasion, and an extensive intraductal component were risk factors for local recurrence. Young age and peritumoral lymphatic invasion also predicted for distant recurrence. This study also provides good evidence that local recurrence and distant metastases are partially interdependent events [1].

A local recurrence may imply either incomplete removal of tumor or it may equate to tumor aggressiveness. The former argument is supported by studies that show lesser surgical approaches may result in enhanced rate of local recurrence. On the other hand, the idea that local recurrence is the result of tumor aggressiveness is supported by the fact that women who have a local recurrence are at three-times increased risk for developing distant metastasis. If local recurrence equates to tumor aggressiveness, then local recurrence and distant metastatic potential should be associated with the same prognostic markers, which is only partially the case [1]. In fact, both hypotheses are likely to be partially true.

The relationship between local and distant recurrence is complex. The timing of local recurrence and distant metastasis differ. The yearly probability for local recurrence is 1% each year for the first 10 years, and for distant metastasis, 5% in the 2nd year, decreasing until the 8th year.[1] The earlier a local recurrence appears, the higher the risk of distant metastasis.[1] If local recurrence is linked to distant spread, opportunities exist to initiate aggressive systemic therapy. When local recurrence is linked to inadequate initial local therapy, local management may be instituted.

Factors that do not have an impact on local regional recurrence include the resection volume[3] or the need for multiple re-excisions[4]. Also histologic subtype (that is recognition of special type carcinomas) does not protect against local recurrence, as shown by Thurman et al. They compared the local recurrence rate of 20 patients with either Stage 1 or Stage 2 mucinous, medullary, and tubular carcinoma with the recurrence rate of more than 1000 patients with invasive carcinoma of no special time. Factors associated with local failure included young age, positive surgical margins, lymphovascular invasion, and tumors with an extensive intraductal component. Regional, distant, or opposite breast failure was associated with Stage 2 tumors, those patients with 4 or more positive lymph nodes, and lymphovascular invasive carcinomas.[5]

Histologic type of breast carcinoma does not preclude breast conservation. Conservative surgery and radiation therapy is equally effective for invasive lobular carcinoma as it is for carcinomas of no special type (invasive ductal carcinoma).[6] The role of lobular carcinoma *in situ* as a predictor of risk of recurrence has been evaluated by Abner, et al.[7] The presence of LCIS within the excision specimen did not have an impact on the risk of recurrence. Furthermore, having LCIS at a margin does not affect local recurrence.[8]

Notes

Much of the emphasis of local regional recurrence has focused on breast conservation approaches. Buchanan, et al. have presented data regarding the risk of loco-regional recurrence after mastectomy. Almost three percent of women developed a local regional recurrence and remained free of distant disease during the study. Factors associated with isolated local regional recurrence included young age (younger than 35), lymphovascular invasion, and multicentricity [9].

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Sponsored by AstraZeneca Oncology

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Current status of tumour receptor analysis

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Breast cancer is now well recognised to be a heterogeneous disease and the role of the pathologist in determining the status of a variety of tumour markers, in order to direct the most appropriate therapy, is fundamental and ever expanding. Hormonal therapy in oestrogen receptor (ER) and progesterone receptor (PR)– positive breast carcinomas is routine and there is now established benefit of specific HER2 – receptor (human epidermal growth factor 2 receptor) targeted therapy in both early and metastatic breast cancers expressing the HER2 receptor and/ or showing HER2 gene amplification.

Immunohistochemistry (IHC) is utilised routinely to assess ER and PR status and is typically reported as a percentage of tumour nuclei stained. This is a predictive biomarker and is utilised to determine eligibility for anti – oestrogen therapy, but there is no universally accepted scoring method or "cut off" for reporting a tumour as "ER/PR positive". Although >10% of tumour nuclei stained is traditionally regarded as a positive result, recent data suggests even patients with as low as 1% of cells stained may benefit from endocrine therapy. A wide variation in the reported results for individual laboratories, however, has been published by the Royal College of Pathologists of Australasia Quality Assurance Program which assesses immunohistochemical staining of ER and PR in Australian laboratories.

The HER2/neu oncogene encodes a transmembrane receptor protein which is a member of the epidermal growth factor receptor (EGFR) family. There is no known ligand for the HER2 receptor but on formation of heterodimers with other members of the EGFR family signal transduction occurs facilitating cell proliferation. A number of methods of HER2 receptor analysis are commercially available. The gold standard is FISH (fluorescence in situ hybridisation) which assesses gene amplification but has limited use in a routine pathology laboratory due to the expense, requirement for a fluorescence microscope and the non-permanent nature of the stains. Immunohistochemical methods, which assess cell surface receptor protein expression, have been widely used and are relatively easily performed but require critical interpretation by a pathologist familiar with the methodology and the criteria for a "positive" 3+ assay. There is a real potential for overstaining / overinterpretation and hence "false positives" resulting in inappropriate treatment of patients whose cancers are not truly HER2 gene amplified. Chromogenic in situ hybridisation (CISH) techniques (Invitrogen Spotlight – manual) were judiciously introduced to 8 Australian laboratories in 2006 though a standardised ISH testing program sponsored by Roche and overseen by members of the Australian HER2 Testing Advisory Board. A stringent set of criteria were determined to demonstrate proficiency by both the laboratory performing the test and the pathologists reporting on the cancers. The CISH technique allows detection of gene copies by regular bright field microscopy and in effect combines in situ hybridisation and immunohistochemistry methodology utilising a Digoxigenin – labelled HER2 dsDNA probe which binds to the HER2 gene locus on Chromosome 17q12-21. The probe is visualised with an immunoperoxidase reaction (Diaminobenzidine – DAB). In addition a biotin – labelled Chromosome 17 centromeric probe may be utilised as a single probe or by dual staining with the HER2 probe (Dako DuoCISH – semiautomated). Subsequently, silver ISH (SISH) a similar but new technology (Ventana Inform – automated), was developed. This technique utilises silver as a chromogen in place of DAB and both techniques show high concordance with FISH controls and with IHC. The ISH reference laboratories could choose their preferred bright field ISH assay. ISH testing for HER2 may be adopted by any laboratory but funding is linked to certification by demonstration of competence and performance of a minimum of 150 tests a year. Similarly, pathologists reporting ISH in breast cancers must be accredited which requires initial comprehensive testing, interval testing and the reporting of at least 50 cases per year, in addition to enrolment in the RCPA CISH Quality Assurance Program. There are currently 23 laboratories taking part in this National HER2 ISH Testing Program with the aim of maintaining a consistent standard. Almost 20,000 ISH tests have been performed. In equivocal cases FISH analysis remains the "gold standard" and St Vincent's Hospital, Sydney, is funded by Roche as the Australian FISH reference laboratory.

National HER2 positivity rates vary from 11-19%. As the testing criteria have become more stringent and the techniques refined the previous reported percentage of HER2 positive tumours in the population has decreased from approximately 25 – 30% to approximately 15%. Thus the majority of cases which tested 2+ on IHC are now considered to represent "false positive" cases in terms of therapeutic significance as only approximately 20% of 2+ tumours showed gene amplification by ISH techniques. However, many laboratories continue to use IHC testing in addition to an ISH technique to provide a second tier assessment and to screen for tumour heterogeneity. There are well defined algorithms for HER2 testing in both early breast cancer

and metastatic breast cancer. ISH testing is now required prior to Pharmaceutical Benefits – linked funding for treatment of HER2 positive early breast cancers with Herceptin. Either IHC3+ or positive chromogenic or fluourescence results are acceptable by Medicare Australia for accessing Herceptin in metastatic disease. However, ISH positivity is required for treatment of metastatic breast cancer with Lapatinib (GSK).

It is likely other targeted therapies will be developed in the future and testing techniques will need to provide prognostic and predictive information to accurately identify these biomarkers and those patients likely to benefit from any therapy. Such markers include the "basal markers", other growth factor receptors and VEGF (vascular endothelial growth factor).

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Notes

Challenges in population screening in Australia

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BreastScreen Australia has overcome huge challenges since commencement in 1991. These achievements have resulted from the hard work and genuine esprit-de-corps of the BreastScreen workforce, from administration to coalface. In the face of many difficulties encountered, achievements include:

- delivering biennial screening mammography and assessment services to almost 60% of women in the target group through a vast terrain
- leadership in quality imaging and guided biopsy and in providing in-service training
- establishment of the multidisciplinary approach, now a model for other cancer control strategies
- attaining, largely, the major clinical outcomes of the program, including small cancer detection at accreditation rates and higher
- achieving a high level of acceptance by women and the medical profession
- reducing breast cancer mortality

Fortunately the program was established with the essential features of two view biennial mammography screening, double reporting and a structure emphasising client support and education. However, the program has shortcomings, which include:

- chronic shortages of key service personnel
- absence of training at inception or in-service for many key clinical personnel
- no mechanism for evaluation of radiologist performance apart from the quarterly audit: this remains the only quality check for the most important criteria of the program- screening sensitivity
- variation in reader quality - the frequency of cancers detected by one of two readers is much higher than expected from the literature
- underutilisation of the vast database of BreastScreen as a research resource
- dense breast tissue severely limits program effectiveness
- women with family history and other risk factors may be screened at inappropriate intervals
- women from ethnic backgrounds are under-screened
- unquantified and unmonitored screening still occurring under Medicare

BreastScreen has recently undergone an extensive review by the BreastScreen Australia Expert Advisory Committee (BSAEAC). At the time of writing the recommendations of BSAEAC are not in the public domain. We can expect broad ranging discussion and recommendations regarding the effectiveness of program in meeting the founding aims and objectives, the costs and benefits identified, consideration of the target age group and workforce, capacity considerations and utilisation of new technology, particularly digital mammography, PACS and teleradiology, among other issues.

MRI features of cancers in high risk women and BRCA1 and BRCA2 carriers

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All international studies of screening women at high risk of breast cancer have demonstrated that MRI has a superior sensitivity for cancer detection than mammography. In studies from the UK, Holland, Canada, Germany and Italy, MRI sensitivity with annual surveillance varies from 71-94% compared to mammographic sensitivity of 33-59% [1-5]. The UK MARIBS trial demonstrated that the difference in sensitivity was most marked in women with a *BRCA1* gene mutation with MRI shown to have the highest sensitivity compared to mammography (92% compared to 23%) [1]. The majority of *BRCA1* cancers are of basal phenotype and there is increasing concern that this pathological subtype will have a particularly poor prognosis [6,7]. There have been a number of studies comparing survival of women with basal phenotype with a non-basal phenotype and these suggest that the traditional expectation that smaller cancers will have improved survival does not seem to hold. It is imperative that these cancers are detected when they are very small before the tumours have metastasized to lymph nodes or other areas of the body. *BRCA2* cancers are more likely to be similar in pathological appearance to sporadic cancers and DCIS is common.[7]

The imaging features of these cancers found in mutation carriers and family history groups have been reviewed to ascertain whether there are different features which suggest cancer and allow earlier detection. Review of cancers found in high risk women indicates that only 38% had suspicious MRI imaging features compared to 71% in a control group.[8] Reviewing the Dutch data, *BRCA1* and *BRCA2* carriers were frequently found to have benign morphological features with round shape and sharp margins although 82% had a type 3 malignant washout curve.[9] Up to 30% of invasive cancers found on MRI in a high risk group had smooth margins with a round or oval shape and 24% had benign kinetic features.[10]

Review of the cancers found in the UK MARIBS study found that the MR imaging features are typical of invasive cancers and show poorly defined, irregular or spiculated margins, have predominantly ring like or heterogeneous enhancement patterns and type 2 or 3 enhancement curves [11]. There was no difference in MRI morphological or enhancement characteristics between the genetic subgroups. The tumour sizes detected by MRI and mammography were not significantly different. The *BRCA1* cancers found by MRI tended to be smaller than those detected by mammography (median 17 mm vs 30 mm, p=0.37), whereas the opposite was true for *BRCA2* (MRI median size=12.5 mm vs mammography median 6 mm, p=0.067), neither statistically significant. Cancers on prior examination were of smaller size, showed less enhancement and were more likely to have a type 1 enhancement curve compared to those cancers on the subsequent diagnostic screen. Tumours with prior MRI abnormalities grew at an average of 5.1mm/year. Comparing the pathological size of invasive cancers found in incident rounds only, *BRCA1* cancers were an average of 19 mm and *BRCA2* 8 mm and invasive cancers from patients with no identifiable mutation were an average of 19 mm. This suggests that *BRCA1* cancers may grow more rapidly or that *BRCA2* cancers are more easily detected by mammography or MRI. This has been demonstrated previously in the Dutch cohort [12] and when the tumors from the Dutch, Canadian and UK trials were combined.[13] It may be that the year long screening interval allowed these cancers to grow to a substantial size.

Multifocal or multi centric disease was not found in the UK study on either MRI or mammography. This contrasts with the German and Italian studies where multifocal or multi centric or bilateral disease was found in 44% and 50% respectively of cases [4, 5]. The reason for this difference is not apparent. The reported pathological characteristics of the cohorts appear similar, although the Canadian and Italian women were older. The German, Canadian and Italian studies also included women with a personal history of breast cancer as well as familial risk which may have affected the rate of multifocality. However, in the Italian study of 9 cases with multifocal/centric or bilateral disease only three had a previous history of breast cancer.

The UK study reviewed the MRI features of abnormalities found on prior examinations of 12 screen detected cancers. These tumors increased in size over subsequent examinations with an average increase of 5.1 mm each year accompanied in general, by an increasing amount of signal change following intravenous contrast enhancement. This may be partly due to a partial volume effect in the smaller cancers on prior examination due to slice thickness. Larger tumors may have larger signal change following contrast enhancement but this was not evident in our study. This signal change may be related to the increasing size of the lesion but other factors such as increasing tumor vascularity and the degree of neoangiogenesis may also be important. It is important that radiologists do not dismiss all small lesions as benign because the signal enhancement is low or there is a benign enhancement curve. When undertaking MRI surveillance in high risk cohorts it is important that attention is paid to any enhancing abnormality. If there is doubt, concurrent and previous mammograms should be reviewed and an ultrasound examination undertaken. If these are negative, a follow up MRI examination within 6 months is recommended or image guided biopsy undertaken for more suspicious cases.

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However, this recommendation has to be balanced against the adverse effect of increasing the recall rate for a screening MRI examination as adopting this policy would lead to a marked increase in false positive examinations.

It is essential that high quality MR examinations are carried out with small voxel size and dynamic contrast enhanced sequences with good temporal parameters with minimum movement between sequences. This may aid the detection of high grade DCIS and small tumours.

Review of the prior MRI examinations in the UK MARIBS study shows that the cancers grow in size, change from type 1 to type 2 or 3 enhancement curves and demonstrate greater signal enhancement over time. It is essential in high risk screening to be vigilant about these small cancers and to maintain a high degree of suspicion.

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Using evidence to select systemic therapy

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Notes

Overall mortality due to breast cancer has dropped dramatically in the Western World over the last 30 years. Although screening has contributed to this decline, adjuvant systemic therapy has been a major contributor[1]. Therefore, in order to ensure that this trend continues, one might argue that all patients should be treated with all therapies. However, such a strategy would clearly result in gross over-treatment, with consequent unnecessary costs and toxicities.

"Personalized Cancer Care" was the theme of this year's ASCO meeting, chosen by President Richard Schilsky. Personalized care will only occur when reliable and accurate markers are available that predict risk of remaining free of or suffering from cancer recurrence (prognosis), sensitivity or resistance to therapy (prediction), and tolerance or toxicities from treatment. Sadly, most investigations of markers that might result in individualized therapy are studies of convenience, in which an assay that is often not technically stable and specimens that have been archived under variable circumstances are available. Unlike rigorous laboratory-based or prospective clinical trial studies, these studies of convenience are likely to produce highly confounded, and frankly unbelievable, results[2]. The ASCO Tumor Guidelines Committee, and others, have proposed systematic criteria for grading the evidence of tumor marker results, and have based recommendations for breast and GI cancer marker clinical use[3-5].

In that regard, the recommendations for breast cancer markers have been quite conservative. The ASCO Guidelines Committee has recommended use of estrogen receptor (ER) and progesterone receptor (PgR) for selection of endocrine treatments in the adjuvant and metastatic settings, HER2 for selection of anti-HER2 therapies (trastuzumab, lapatinib), and the rtPCR-based 21 gene recurrence score and an enzyme-based immunosorbant assay for PAI1 and UPA to establish favorable prognosis and avoid adjuvant chemotherapy in node negative, ER positive breast cancer patients. The Committee also recommended MUC1 assays (CA15-3 or CA27.29) and assays for carcinoembryonic antigen (CEA) to monitor patients with established metastatic disease[4].

There are three components for determination if a tumor marker should be used clinically:

- What is the precise clinical use? Is it for risk categorization or screening of higher risk but unaffected subjects, Is it for differential diagnosis, prognosis or prediction of benefit from a specific therapy? Is it to monitor patients during treatment or to detect occult recurrence. And, is there evidence that knowing this information results in improvement in clinical outcome?
- What is the magnitude of difference in outcome between patients who are "positive" vs. those who are not? A p value of 0.05 does not establish clinical utility, it only signifies that one group is likely to be different than the other. Rather, one wants to find groups whose outcomes are so disparate for the use described above that, if the estimate of difference is likely to be real, one would treat one group differently than the other.
    - Is the estimate of that difference reliable?
    - Is the assay technically reliable?
    - Has the study been designed prospectively to accurately address the clinical use?
    - Have the results been validated in a separate, but equally well-designed trial?

Having established these principles, several encouraging efforts have led to improved use of tumor markers in breast cancer. In addition to the Guidelines Committee deliberations discussed above, ASCO and the College of American Pathologists have partnered to address the technical aspects of assaying HER2, establishing proficiency testing necessary to receive CAP accreditation[6]. A similar initiative to address ER is now underway.

Additionally, several prospective randomized clinical trials are underway in which a tumor marker is specifically the primary objective of the trial. These include SWOG S0500 to test the utility of circulating tumor markers in metastatic breast cancer, and the TAILORX and MINDACT trials in the US and Europe to test the utility of multi-gene assays in identifying those node negative, ER positive patients who might benefit from adjuvant chemotherapy. Likewise, the Southwest Oncology Group has reported that the 21 gene recurrence score assay may identify node POSITIVE, ER positive patients who, although their prognosis is relatively poor, may have chemo-resistant tumors[7]. A large PRCT is under development to test this hypothesis.

In summary, cancer diagnostics should be valued as much as cancer therapeutics. A bad tumor marker is as bad as a bad drug, and a diagnostic should not be used unless one is reasonably certain that the results permit one to make a decision from which the patient will benefit. Sadly, this is all too rare.

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Optimal adjuvant endocrine therapy for early breast cancer

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Notes

Adjuvant endocrine therapy (AET) significantly reduces both recurrence and mortality in early breast cancer (EBC) in patients with hormone receptor positive tumours (i.e. oestrogen (ER) and/or progesterone (PgR) receptor positive tumours). Oophorectomy was the first form of AET for EBC, but is only effective in premenopausal patients. Tamoxifen was introduced in the early 1970s and replaced oophorectomy in premenopausal patients but is also equally effective in postmenopausal patients. It is not yet known whether ovarian ablation or suppression plus tamoxifen improves outcomes compared with tamoxifen alone in premenopausal women, or whether ovarian ablation or suppression plus an aromatase inhibitor might be even more effective. Several large international studies are currently addressing these and other questions regarding the optimal hormonal therapy for premenopausal women with EBC.

More recently, the aromatase inhibitors have become available for the treatment of postmenopausal women with hormone receptor positive EBC. Studies have consistently shown improved outcomes with aromatase inhibitors over tamoxifen whether they are administered up front, instead of tamoxifen, or sequentially, after 2-3 years of tamoxifen. Postmenopausal patients deemed at moderate or high risk of recurrence should be offered an aromatase inhibitor as initial therapy rather than tamoxifen, providing there is no contraindication, such as osteoporosis. For patients deemed at low risk of recurrence, the selection of appropriate initial hormonal therapy requires assessment of the patients' other medical issues and co-morbidities and a balance of the potential side effects of tamoxifen compared with an aromatase inhibitor.

The optimal duration of AET has not been established. However, the standard duration of tamoxifen is five years as previous studies have shown that five years of tamoxifen is associated with better outcomes than shorter durations. Preliminary results from the ATLAS trial suggest that more than five years of tamoxifen is associated with a significantly lower recurrence rate than only five years of tamoxifen. However, in contradistinction, the NSABP B14 trial showed no additional benefit from more than five years of tamoxifen in node negative patients with EBC. The MA17 trial which examined the role of letrozole as extended adjuvant therapy after five years of tamoxifen showed a significant improvement in disease free survival in both node negative and node positive patients and a significant improvement in overall survival but only in node positive patients. Thus, it is likely that more than five years of AET will become standard, in appropriate patients.

Sponsored by Novartis Oncology

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MD Anderson approach to neoadjuvant therapy

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The Early Breast Cancer Trialists' Collaborative Group overview analysis of adjuvant chemotherapy demonstrated reductions in the odds of recurrence and of death in women age 70 years or younger with stage I, IIa, or IIb breast cancer. Adjuvant chemotherapy is currently recommended for patients with invasive cancer greater than 1.0 cm in size and considered for those with smaller tumors and adverse prognostic factors (lymphovascular invasion, high nuclear grade, high histologic grade, HER-2/neu overexpression, negative hormone receptor status).

Neoadjuvant (or preoperative) chemotherapy, has traditionally been administered in cases of inoperable or locally advanced disease to facilitate local-regional treatment with surgery and radiation. The success of this approach, in addition to the known benefits of adjuvant (or postoperative) chemotherapy, has led to the increasing use of neoadjuvant therapy for the treatment of patients with operable breast cancer. In this review the advantages and disadvantages of the neoadjvuant chemotherapy approach are discussed.

Potential benefits of neoadjuvant chemotherapy

Although several studies have demonstrated that breast conserving therapy is feasible after neoadjuvant chemotherapy, the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, clearly demonstrated increased rates of breast conservation in women randomized to neoadjuvant chemotherapy. Patients received 4 cycles of doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) (AC) every 3 weeks and this increased the proportion of patients able to undergo lumpectomy by 12%. At a mean follow-up of 9.5 years, there were no significant differences in disease-free and overall survival rates between the 2 randomized groups (69% vs 70%, $P = .80$; 55% vs 53%, $P = .50$, respectively). Similar results published from other randomized studies, and a recent pooled meta-analysis revealed that both approaches provide equivalent survival outcomes. Therefore, neoadjuvant chemotherapy appears to be a safe alternative to the use of adjuvant therapy, especially in patients in whom breast conservation therapy may not be feasible if surgery is the initial approach.

Another advantage of the neoadjuvant approach is the ability to assess response of the primary breast tumor and any nodal metastases after systemic treatment. Both clinical and pathologic response rates have been shown to be surrogate markers for the traditional endpoints of disease-free survival and overall survival obtained from adjuvant trials. In the European Organisation for Research and Treatment of Cancer (EORTC) 10902 trial, patients with operable disease were randomized to pre- or postoperative therapy with 4 cycles of 5-fluorouracil (600 mg/m^2), epirubicin (60 mg/m^2), and cyclophosphamide (600 mg/m^2) (FEC) every 3 weeks. No significant differences were seen in disease-free and overall survival at 56 months of follow-up, however, in the preoperative chemotherapy group, there were 13 patients who achieved a pathologic complete response (pCR), defined as the absence of invasive cancer in the breast and axillary nodes. When compared with the patients that did not achieve a pCR, there was a statistically improved overall survival with a hazard ratio (HR) of 0.86 (95% confidence interval [CI], 0.77-0.96; $P = .008$). Based on these and other data showing a correlation between pCR and disease-free and overall survival, it appears that pathologic response can be used as a surrogate endpoint of long-term survival. This approach can provide a more rapid evaluation of treatments for patients with early-stage breast cancer.

Symmans and colleagues from the MD Anderson Cancer Center have developed a prognostic model that quantifies residual disease in the breast and nodes (residual cancer burden) after neoadjuvant chemotherapy to determine distant relapse rates at 5 years. This tool has been validated and is currently being used as a surrogate marker for long-term survival endpoints.

The neoadjuvant platform for evaluation of novel biologic agents

The neoadjuvant approach can also facilitate the evaluation of novel biologic agents either alone or in combination with standard chemotherapeutics. Buzdar and colleagues demonstrated superior pCR rates in an MD Anderson trial which compared neoadjuvant paclitaxel-FEC chemotherapy with or without trastuzumab for operable HER2-positive breast cancer. Patients who received chemotherapy concurrently with trastuzumab had pCR rates of almost 65% compared with 25% for those who received chemotherapy alone. These are the highest pCR rates reported to date and support the use of the neoadjuvant setting to screen new agents or novel combinations.

In addition to targeted treatment trials with specific biologic agents, investigators are currently using gene-expression profiling to determine pCR rates. There have now been several reports of in vitro chemosensitivity gene expression signatures, which can predict response to neoadjuvant chemotherapy with high degrees of sensitivity and specificity. A similar concept is being tested with neoadjuvant endocrine therapy in patients with hormone receptor-positive disease in the American College of Surgeons Oncology Group Z1031 trial. Patients are randomized to receive 1 of 3 aromatase inhibitors for 16 weeks prior to surgical resection. Pre and post treatment samples are obtained and gene expression profiling is being performed with the goal of developing profiles that can predict resistance to endocrine therapies.

The neoadjuvant therapy approach has the potential to allow individualization of cancer therapies through the use of gene expression profiling of tumors and assessment of pathologic response rates. This approach can expedite evaluation of novel therapies with the surrogate endpoints for survival of pCR and residual cancer burden, without the need for long-term follow-up typically required in adjuvant treatment trials.

Potential pitfalls of neoadjuvant chemotherapy

Although neoadjuvant chemotherapy allows for assessment of individual response to therapeutics, the ability to tailor systemic treatments based on the clinical response in the breast and regional nodes has not yet been proven as an effective strategy. Trials that have utilized clinical response or pCR rates to determine the benefit of additional chemotherapy, particularly for nonresponders, have not shown any statistical improvement between responders or nonresponders switched to different regimens. Using clinical response early on may spare patients the toxicities of ineffective therapies that they would have received in the adjuvant setting, although the safety of this approach has not been established. The major question remains as to what additional treatments, if any, should be administered to patients who continue to have significant residual disease after neoadjuvant chemotherapy. There is an ongoing NSABP trial assessing the use of biologic therapy in patients who have significant residual disease following chemotherapy.

Impact of neoadjuvant chemotherapy on rocal-regional therapies

Some early neoadjuvant chemotherapy trials used core needle biopsy to assess for residual disease in the breast prior to any planned resection of the tumor bed. This approach was associated with high in-breast recurrence rates even when high-dose radiotherapy was delivered to the whole breast. There is currently no consensus on the volume of tissue that should be resected following neoadjuvant chemotherapy. However, volume of resection can clearly impact cosmetic outcomes and there is no data to suggest that the entire pretreatment tumor volume should be resected for improved breast cancer outcomes. Placing radiopaque clips at the primary tumor site prior to chemotherapy can facilitate the appropriate targeting of any residual nidus of tumor after treatment. At MD Anderson we have established specific clinical and radiographic parameters that should be assessed before and after chemotherapy prior to offering patients breast conservation therapy after chemotherapy. We recently reported our experience with breast conservation after chemotherapy and found that 5-year actuarial ipsilateral breast tumor recurrence-free survival and local-regional recurrence-free survival rates were 95% and 91%, respectively. Factors correlating with ipsilateral breast tumor recurrence and local-regional recurrence were clinical N2 or N3 disease, pathologic residual tumor size > 2 cm, a multifocal pattern of residual disease, and lymphovascular space invasion. We subsequently developed a prognostic scoring index with these factors that can be used to assist clinicians in counseling their patients regarding the use of breast conservation therapy after chemotherapy.

Axillary lymph node dissection (ALND) has been routinely performed for the management of the axilla following neoadjuvant chemotherapy. As sentinel lymph node (SLN) surgery has increasingly gained acceptance and reduced the need for ALND in early stage node-negative patients, surgeons have begun to incorporate this technique in the management of patients after chemotherapy. This strategy allows patients to undergo one operative procedure at the completion of chemotherapy with assessment of pathologic response in the breast and nodes. A number of institutions have demonstrated the feasibility of SLN surgery following chemotherapy, and a recent meta-analysis reported an overall accuracy rate of 94%, sensitivity of 88%, negative predictive value of 90%, and SLN identification rate of 90%. Based on available data, SLN surgery appears to be feasible in node negative patients but is not yet proven accurate in patients with node-positive disease at presentation.

A local-regional treatment decision that can be more difficult after neoadjuvant chemotherapy is the use of postmastectomy radiation therapy (PMRT). Currently, indications for PMRT are based on pathologic factors determined at surgery, including tumor size and number of positive nodes. Because chemotherapy will alter the extent of disease in the breast and nodes depending on response in each patient, the indications for PMRT can be blurred. Buchholz and colleagues from MD Anderson evaluated local-regional recurrence rates following neoadjuvant

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chemotherapy and found that both initial clinical stage and extent of residual disease following treatment are important factors. We currently recommend PMRT for patients with stage III disease at presentation and consideration for stage II patients who have 1 to 3 positive nodes after chemotherapy.

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Conclusions

Neoadjuvant chemotherapy is an established approach for patients with inoperable and locally advanced disease at presentation. It has the potential to improve surgical options in some operable breast cancer patients and is an important tool for evaluating novel therapeutics in select subsets. The neoadjuvant approach allows for the pathologic assessment of systemic therapies on tumor biology which can also provide information on expected outcomes for individual patients.

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Monitoring neo-adjuvant chemotherapy

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Notes

There has been recognition of the potential importance of imaging biomarkers to personalize treatment for patients with cancer. MRI has the capacity to predict response to treatment and also assess response to neo-adjuvant chemotherapy. There is a considerable body of literature reporting the use of MRI for monitoring neo-adjuvant chemotherapy in women with locally advanced breast cancer. However most studies are small and use variable acquisition and analysis techniques with inconsistent endpoints making it difficult to assess the value or reproducibility of this modality and the value to the clinician for patient management. There is agreement that MRI is superior to clinical examination, mammography and ultrasound in assessing disease extent on completion of chemotherapy in order to plan surgery[1,2] although this technique cannot detect small residual foci of viable tumour cells [3]. An American review included 18 studies and showed that MRI consistently had a sensitivity of 90-100% and specificity of 50-100% in detecting residual disease using histopathology as the gold standard. In five of the studies the actual size and disease extent was compared with final histopathology and the accuracy varied between 57-97% with correlation co-efficient of 0.72-0.98. MRI was accurate in determining whether there was chest wall involvement. A study of 68 patients compared the final histological size to clinical examination, ultrasound and MRI. The correlation co-efficient was 0.439, 0.612 and 0.749 respectively [4]. However the MRI results may be less accurate after anti-angiogenic agents [5]. The recurrence rates after neoadjuvant chemotherapy can be high and a small series reported 10 % local recurrence rate by 18 months in patients who had pre-operative staging by MRI [6].

Studies have been undertaken to ascertain whether any of the MRI parameters could be used to predict response to treatment but so far none have found to be useful. A reliable assessment of lack of response would allow the oncologist to switch to a more effective chemotherapy regime earlier in patient management. Changes in tumour size have been assessed with Wasser et al showing a correlation with response after 3 cycles of chemotherapy and Yu et al and Padhani A et al reporting a significant correlation with change in tumour size after one course of chemotherapy[7-9]. Cheung and colleagues demonstrated that a 8.8% reduction in maximum tumour dimension could be used as a cut off to predict response to therapy after one course of chemotherapy [10]. Several studies have shown a reduction of the tumour vascularity, as measured by slower and less contrast enhancement, to precede a reduction in measurable tumour volume. The Blue Cross Shield review of 6 studies assessing the value of MRI in monitoring treatment found results inconsistent, low patient numbers with only two of the studies reporting a negative predictive value of 58% and 83% in identifying those patients who were not responding to chemotherapy. Some of the patients who did not show any response after two courses of treatment went onto have at least a partial response.

Further work in this area would be valuable with agreed methods to assess response on MRI. Reproducibility of this technique is required before Pharma or the FDA will accept this method as a surrogate endpoint of response. The US National Cancer Institute is funding an initiative in imaging biomarkers in an attempt to agree methodological issues for acquisition and analysis of MR data aimed at prediction of response or assessment of response to chemotherapy (Quantitative Imaging Biomarker Alliance). Input is sought from a variety of societies including medical physics, radiology, MR groups and Pharma to come to an acceptable international consensus.

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Neoadjuvant endocrine therapy or chemotherapy

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Notes

The role of pre-operative chemotherapy in locally advanced breast cancer is firmly established. There is now also an emerging role for primary systemic (neoadjuvant) therapy in the treatment of operable breast cancer. There is good evidence from randomised trials that pre-operative therapy results in tumour downstaging and increases the likelihood of breast conserving therapy. Results of randomised studies indicate that survival is at least as good with neoadjuvant as with adjuvant chemotherapy.[1] Trials would also suggest that up to 40% of patients can avoid mastectomy with pre-operative aromatase inhibitor therapy.[2]

Pathological complete response (pCR) to neoadjuvant therapy has emerged as an important predictor of subsequent outcome. Indeed many of the current raft of neoadjuvant chemotherapy trials in early breast cancer have pCR as their primary endpoint.[3] Pathological involvement of axillary nodes following neoadjuvant therapy portends a poor prognosis.

With the identification of distinct phenotypic and genomic subtypes of breast cancer the opportunity to tailor therapy to the tumour has emerged. Triple negative breast cancers and BRCA1/2 mutated breast cancer have particularly high response rates (up to 88%) to neoadjuvant platinum-based chemotherapy.[3] The use of neoadjuvant trastuzumab in HER2-positive breast cancer has resulted in 37-45% complete response rates.[4]

For the future, there are important potential advantages in having an in vivo measure of chemosensitivity rather than blindly treating micrometastatic disease in the adjuvant setting. The potential for biological surrogate markers of response to predict for long-term outcome may allow individualisation of systemic treatment and the rapid assessment of new drugs in early breast cancer.

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Notes

Ten years of a breast cancer database in the ACT and SE NSW

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In 1997, a database for newly diagnosed patients with breast cancer in the ACT and the surrounding area of SE NSW was established. The database was approved by the ACT Health Human Research Ethics Committee. From 01/07/1997-30/06/2007, a total of 2829 patients were entered, representing approximately 96% of all newly diagnosed breast cancers in the region. A total of 2371 women (84%) had unilateral invasive disease, 293 women (10%) had DCIS, 58 women (2%) had bilateral synchronous breast cancer, 49 women (2%) had metastatic disease at presentation, 19 (<1%) were male and 39 (1%) women did not have surgery. Of the 2371 patients with unilateral invasive disease, 1157 (49%) had breast conserving surgery (BCS) and 1214 (51%) had a mastectomy (Mx). The majority of patients only underwent one surgical procedure. Of the women who had BCS, 1099 (95%) received radiotherapy (RT) compared with 457 (38%) of the Mx patients. Of the 2371 patients with unilateral invasive disease, 1229 (52%) received adjuvant chemotherapy and 1846 (78%) received adjuvant endocrine therapy (AET), predominantly with tamoxifen.

There were clear changes in the pattern of practice over the course of time. Core biopsy and vacuum assisted core biopsy have largely replaced the use of fine needle aspiration cytology in the diagnosis of both in situ and invasive disease. Sentinel lymph node (SLN) biopsy was introduced in 1999 and since then there has been a rapid rise in the number of SLN biopsies performed in the ACT, although significantly fewer SLN biopsies were performed in SE NSW. Recently, breast MRI has become available in the ACT.

Women with screen detected cancers were more likely to have BCS and a SLN biopsy as their only surgical interventions. With respect to adjuvant therapies, a higher proportion of patients under the age of 60 years received adjuvant chemotherapy than patients 60 years or older. Initially, CMF was the most commonly used chemotherapy regimen, but anthracycline based regimens and more recently taxane based regimens have generally replaced the use of CMF. Herceptin usage began in 2004-2005. With respect to AET, the number of patients who received an aromatase inhibitor has increased significantly since 2002.

With a median follow up of six years, 1907 (81%) of the 2371 patients with unilateral invasive disease remain alive and free from relapse. Two hundred and seventy-one patients (11%) have died and in 176 (7%) this was confirmed to be due to breast cancer. Seventy-one patients (3%) remain alive, but with recurrent disease. A total of 122 patients (5%) have been lost to follow up.

There was high concordance of treatment received with published guidelines. However, patients in SE NSW were less likely to receive radiotherapy after BCS, than patients in the ACT. Overall, the proportion of patients who remain alive and disease free is high. During the existence of this database, SLN biopsy, anthracycline and taxane based regimens and Herceptin have been introduced into routine practice.

Breast clinic triage tool: A 4-item questionnaire for telephone assessment of new referrals

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Notes

Background

Public awareness of the high incidence of breast cancer has increased referrals to specialist breast clinics. The proportion of patients with benign rather than malignant conditions has increased in many centres, reducing the efficiency of clinics in assessing and treating women with breast cancer. An effective method of triage for new referrals may be used with the aim of increasing efficiency in the assessment and treatment of cancer patients and maximising use of clinic resources.

Aim

To review the literature on triage processes, to audit recent referrals to our breast clinic and to use these results to develop a telephone triage tool. The tool will be used by breast clinic administration staff to determine both the urgency of new referrals and the appropriate medical practitioner (surgeon or breast physician) to conduct the initial consultation.

Methods

A literature review identified and evaluated several breast clinic triage tools. An audit of recent referrals to our breast clinic determined the most common reasons for referral and the number of benign and malignant diagnoses. The accumulated information was used to develop a triage tool.

Results

Three triage tools were reported in the literature. Audit of 371 consecutive referrals (108 cancers) identified 295 referrals from general practitioners and 62 from BreastScreen. The most common reasons for referral were 'breast lump', 'BIRADS 4/5 imaging abnormality' and 'mastalgia.' Presenting symptoms with the highest likelihood of a malignant diagnosis were 'BIRADS 4/5 imaging abnormality' ($p<0.001$), signs of 'locally advanced breast cancer' ($p=0.004$) and 'breast lump' ($p=0.539$). Based upon this data, a 4-question triage tool was designed by a multidisciplinary team for use by administration staff during the telephone interview when new patients first make contact with the clinic.

Conclusion

A triage tool has been developed and is ready for implementation and evaluation.

Notes

Is breast self examination (BSE) still relevant in detecting breast cancer?

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Background and purpose

Breast self examination BSE) is the easiest, at no cost and a useful practice to raise women's awareness of changes in their breast and body. The National Health Morbidity Survey in 2006 showed that the screening rate by breast self examination (BSE) and clinical breast examinations (CBE) was 57% and 52%, respectively. This study aims to determine the rate of BSE practise and whether BSE is still relevant in detecting breast cancer.

Methods

This was cross sectional study whereby pretested questionnaires were posted to all female staff of University Malaya, aged 40 years and above. Their knowledge on breast cancer and practice of BSE were evaluated. History of attending CBE and detection of breast lump was elicited.

Results

The response rate for this study was 48 percent (539 out of 1132 questionnaires posted). The rate of respondents having awareness on breast cancer was 98.7 percent. Eighty four percent (454) of the respondents had done BSE in their lifetime. However, only 12.0 percent performed regular BSE at the recommended time. Sixty two percent (334) had undergone at least one CBE while 30.8% (165) had done mammogram. There was significant relationship between CBE and BSE whereby those who had CBE were twice more likely to do BSE than those who never had CBE. Nineteen percent (84 respondents) of those who did BSE claimed they had detected breast lump and were confirmed to have breast lump on further check up by the healthcare workers. Of these, 7 (8.3%) had treatment for breast cancer while those with benign breast lump had surgical lump removal.

Conclusion

BSE is still relevant to detect breast cancer. CBE should be done to all women at risk of breast cancer to encourage and teach BSE.

Factors influencing treatment recommendations in node-negative breast cancer

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Notes

Background and purpose

An increasing number of women are diagnosed with stage 1 breast cancer and indications for adjuvant chemotherapy (CT) have broadened to include patients with node-negative (N0) disease in the presence of other adverse features. This survey aimed to assess factors influencing recommendations for CT in N0 patients.

Methods

Review of 2007 and 2008 postoperative breast cancer patients discussed at Royal North Shore Hospital multidisciplinary team meetings. Patient summaries contain demographic, clinical, comorbidity, psychosocial and pathology data and recommendations for adjuvant therapy. Estimated benefits of adjuvant CT on 10-year survival, assuming use of a second-generation agent for N0 patients, were calculated using Adjuvant! Online. Univariate and multivariate analyses were performed using SPSS.

Results

Of 447 patients discussed, 102 were excluded; 26 recurrent disease, 62 DCIS, 2 unknown nodal status and 12 neoadjuvant therapy. Of the remaining 345, mean age was 59 and 51 were unsuitable for CT through comorbidity / age >80. Of those fit for CT, 93 of 94 (99%) with node-positive disease and 20 of 25 (80%) with nodal micrometastases were recommended CT. For N0 patients, 94 of 175 (53%) were recommended CT; tumour size >2 cm, higher grade, ER-positivity, HER2-positivity and age <45 years influenced CT recommendations ($p<0.0001$ for each) contributing 70% of the overall effect. Using Adjuvant! Online, the mean benefit of CT in N0 patients receiving this recommendation was 5.7% *vs.*1.3% in patients not recommended CT. Approximately 75% of patients with N0 or Nmic disease accepted a CT recommendation. Patients not choosing CT were advised against CT at a medical oncologist appointment. From 2007 to 2008 recommendations for CT increased (44-59%; $p=0.04$).

Conclusions

For N0 patients, the minimum level of benefit to recommend CT is ~ 2%. Grade, tumour size, ER-status and younger age influence CT recommendations. Micrometastases are being treated more aggressively over time.

Notes

Frozen section for intra-operative detection of nodal metastatic disease in breast cancer

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The aim of the study was to assess the value of intra-operative axillary sentinel lymph node (SLN) assessment by frozen section (FS) in breast cancer in an Australian public hospital setting. Retrospective analysis was undertaken of all patients undergoing frozen section of sentinel lymph biopsy, admitted to St Vincent's Public Hospital, Sydney between 2004 and 2008.

Methods

Sentinel lymph node biopsy was performed in 211 consecutive patients undergoing resection for clinical stage Tis-T3N0 breast cancer. All pathology analysis was undertaken by the St Vincent's Hospital pathology service.

Results

All but 2 patients were female, 161 patients had invasive ductal carcinoma, 22 lobular carcinoma, 16 patients had DCIS and 12 had other tumours.

SLN biopsy was positive in 45 patients. FS detected metastatic disease in 28 patients with a sensitivity of 62%. There were no false positive results by FS. The median size of metastatic disease detected by frozen section was 6.0 mm.

FS produced a false negative result in 17 patients of which 11 had micro-metastatic disease. The median size of metastatic disease not detected by frozen section was 1.0 mm.

The sensitivity of FS rose to 81% when micro-metastatic disease was excluded from analysis.

In our series FS predicted the state of the sentinel node in 92% of patients.

Conclusions

From our experience frozen section is a useful and reliable method to detect intra-operative nodal metastatic disease, however its sensitivity is limited with regards to micro-metastatic deposits.

Reference

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Proscription of deodorants during adjuvant breast radiotherapy: A survey of compliance, patient impact and evidence of safety

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Notes

Background and purpose

Proscription of anti-perspirants or deodorant use during adjuvant breast radiotherapy is considered standard care. The investigators were seeking an information base to justify current practice and facilitate design of an appropriate controlled trial of the use of deodorants during radiotherapy if insufficient evidence to support current practice was found.

Methods

The first component consisted of a survey of women after adjuvant breast radiotherapy seeking information about routine deodorant use and potential concern if deodorants were not permitted during radiotherapy. The second component comprised a literature search for any existing controlled evidence regarding harm from deodorant use during radiotherapy.

Results

414 women completed surveys. 280 recalled advice against deodorants. 299 women routinely used deodorants, 70% of whom used roll-on products. 45 continued deodorant use during radiation, 20 of these despite recalling advice not to wear a deodorant. Of 233 women who routinely wore a deodorant but abstained during radiotherapy, 19% expressed a lot of concern about body odour and 45% were slightly concerned. Odour distress did not correlate with average seasonal maximal temperature or humidity. The literature search revealed 3 controlled studies totalling 310 patients comparing specific (crystal or aluminium-free) deodorants versus no deodorant. These did not show statistically significantly increased skin reactions, but had only a small subset of 51 patients with axillary irradiation.

Conclusions

The proscription of deodorant use during radiotherapy is an historical standard practice of unproven benefit which causes body odour concern to the majority of women who are usual deodorant users. The next most appropriate trial would compare use of usual deodorant versus no deodorant, would encompass a significant number of women with radiotherapy to the axilla or application of deodorant to irradiated skin areas, and include endpoints other than skin reaction alone.

Notes

Historical cross-trial comparisons for competing treatments in advanced breast cancer – an empirical analysis of bias

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Purpose

Randomised controlled trials (RCTs) provide optimal evidence to assess the benefits of new treatments. However, clinicians routinely rely on cross-trial comparisons to assess competing treatments when head-to-head randomised comparisons are not available. We investigate the validity of cross-trial comparisons using individual patient data (IPD) where patients received the same treatment protocol. We also examine the extent statistical adjustment for baseline prognostic characteristics can account for the differences in outcomes observed across trials.

Patients and methods

We used pooled IPD of women with advanced breast cancer assigned to the control arms of three Australian New Zealand Breast Cancer Trials Group RCTs of first-line treatment (8101, 8614, 0001) conducted at different time period. These women were treated with oral cyclophosphamide, intravenous methotrexate and 5-fluouracil (CMF). The Kaplan-Meier method was used to compare progression-free survival (PFS) and overall survival (OS) across trials. Proportional hazard models were constructed to estimate the hazard rates across trials after adjustment for baseline prognostic characteristics.

Results

The distribution of baseline prognostic characteristics varied across trials. There was a statistically significant difference in survival across trials (logrank p=0.009). The median OS was 17.7, 10.3 and 10.1 months for 0001, 8101 and 8614 respectively. The adjusted hazard ratios (AHR) for survival were 1.44 (8614) and 1.45 (8101) as compared to 0001 (p=0.03). PFS did not differ significantly across trials (logrank p=0.38).

Conclusions

Caution should be exercised when interpreting results from historical cross-trial comparisons even if adjustment of baseline prognostic characteristics can be performed. Cross-trial comparisons have some role in identifying and prioritising promising treatments for further investigation; however RCTs are still essential to guide sound clinical practice.

St George Public & Private/ Sutherland Hospitals breast multidisciplinary team (MDT) outcomes 2008

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Notes

Background

Quality assurance in Breast Cancer Care is a dynamic process that is necessary to maintain high clinical standards and improve patient care. Collection of Minimum Data Set items is time consuming and resource intensive.

Methods

An Access Data base was established in 2001 initially to aid breast care nurses to follow new patients referred to the service. A major overhaul in 2005, included minimum Data set items for Breast cancer to be included and Funding by the Cancer Institute NSW in 2007 enabled establishment of protocols, a patient management framework and procedures manuals to be created. Data is collected prospectively at diagnosis of all patients seen by the team and consent given by the patient to discuss treatment recommendations. Further data updates are entered at completion of treatment plans. Data is collected by a Breast Fellow, Breast Care Nurses, Medical Oncologist and a Medical Student. Funding via Medicare provided $17,276/annum for the MDT coordinator to organize the meetings, scan and send treatment plans.

Results

In 2008 there were 343 new patients. 518 patient discussions were held at the MDT. Method of detection, ECOG, Histopathology variables will be presented. Breast conservation was achieved in 68%. Time to Radiotherapy, Time to Chemotherapy and problems discussed.

Conclusions

An Access Data Base provides simple data extraction of outcomes for our Multidisciplinary Breast Team but has its limitations. Better web based tools with simple data interfaces could be developed that would service a broader network allowing Clinicians to monitor outcomes and Health Administrators provide adequate resources.

References

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Notes

Injection augmentation mammoplasty - some recent cases and a review of the literature

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Background and purpose

Breast augmentation for cosmesis is not a recent phenomenon. It can be traced back to the late 1800's, when various substances including fat, olive oil, petroleum jelly and vegetable oils were injected directly into the breast with poor results. Later in the 1950's, injections of the new, apparently chemically inert, liquid silicone commenced. Disfiguring side effects led to its being banned by the FDA in as early as 1965. Although injectable augmentation mammoplasty remains banned in most Western countries, injection of various substances such as silicone, fat and polyacrylamide gel (PAAG), continues in some countries. In our institution we have occasionally encountered imaging of women who have undergone such procedures. Familiarity with their imaging characteristics aids in the interpretation of the breast imaging.

Method

Retrospective review of our recent cases at Royal North Shore Hospital as well as the literature was performed.

Results

We review imaging characteristics of injection mammoplasty with autologous fat, silicone and PAAG. We also review and demonstrate some of the complications which include fibrosis, obscuration of glandular elements and granulomata in the breast and lymph nodes.

Conclusion

Although injection augmentation mammoplasty remains banned in Australia, it is available in several countries. Radiologists may be presented with images from women who have emigrated from these countries or Australian women who have opted to have the procedure overseas. It is therefore important to be familiar with their imaging characteristics and complications.

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The prognostic significance of single hormone receptor positive metastatic breast cancer: An analysis of three randomised phase III trials of aromatase inhibitors

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Notes

In metastatic breast cancer (MBC), both the oestrogen receptor (ER) and the progesterone receptor (PgR) are usually analysed. If either is positive (+), the patient is classed as having a hormone receptor positive tumour and may be offered endocrine therapy, if clinically appropriate. However, in the presence of a positive ER, the prognostic significance of the PgR is unknown.

We have performed a retrospective analysis of the data from a total of 1870 patients entered on to three, international, randomised, controlled, phase III studies of anastrozole or letrozole as second line therapy after first line antioestrogen therapy for MBC. The results of these studies have been published previously.1-3 Data were analysed using SPSS, V16.0. The main outcomes were assessed using Kaplan-Meier analysis, with log rank tests and associated probabilities.

A total of 1870 women entered into the three trials and ER was assessed in 1134 patients (61%) and PgR was assessed in 1009 patients (54%). Predominantly, ER and PgR were assessed by ligand binding assays (85% and 84%, respectively), rather than immunohistochemical assays. Results for both receptors were available in 1010 patients. Thirty-one patients had tumours that were both ER and PgR negative (-) and were excluded. Of the remaining 979, 726 (74%) had tumours that were ER+/PgR+, 213 (22%) had tumours that were ER+/PgR- and 40 (4%) had tumours that were ER-/PgR+.

919 patients were assessable for response. There were no significant differences in clinical benefit (CB) or time to progression (TTP) between patients with ER+/PgR+ tumours and those with single hormone receptor positive tumours (ER+/PgR- or ER-PgR+). However, the median overall survival (OS) was significantly longer for patients with ER+/PgR+ tumours (800 days) than those with single hormone receptor positive tumours (600 days, $p = 0.01$). Similarly, in patients with ER+ tumours, the median OS for those with tumours that were also PgR+ was significantly longer (800 days) than for those with tumours that were PgR- (625 days, $p = 0.02$).

In this series of patients with MBC, although there were no significant differences in CB or TTP, the median OS for those with tumours that were ER+/PgR+ was significantly longer than those with single hormone receptor positive tumours. In patients with ER+ tumours, those who had a tumour that was also PgR+ had a significantly longer median OS than those with PgR- tumours. The PgR status provides important prognostic information for overall survival in patients with MBC and should be assessed routinely.

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Notes

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