206 Invited

The emerging role of surgery

E.J.T. Rutgers[1]. [1]*The Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands*

Traditionally, metastatic breast cancer is not the province of the surgical oncologist, but of the medical and radiation oncologists. This is due to the non-curability of advanced breast cancer, and surgery generally considered being a too 'toxic' procedure for palliation.

Nevertheless, three different clinical situations can be distinguished where surgery may play a role in patients with advanced breast cancer:

1. Loco regional control in patients with primary breast cancer and distant metastasis at primary diagnosis;
2. Loco regional control in patients with advanced locally recurrent breast cancer and known distant disease;
3. Patients with loco regionally controlled breast cancer but with distant metastases.

Is there evidence that surgery is likely to improve outcome in these situations? I do believe there is.

Ad 1. An increasing number of – retrospective comparative – studies do show that complete excision of the primary breast cancer is associated with an improved survival of patients with metastatic breast cancer. All studies point in the same direction with HRs between 0.5 and 0.63 in favour of those patients who had their cancers completely excised. This is – very – promising, but these results may very well be confounded by selection bias.

Ad 2. In selected patients with extensive loco regional relapse in the presence of distant disease, even extensive surgical procedures with autologous tissue closure may offer important palliation. On average in a number of studies, in over half of the patients local control for life is achieved with a median survival of 25−30 months, not much different from patients without apparent distant disease.

Ad 3. Many studies describe the results of selected patient groups after resection of −mostly isolated or very limited pulmonary or liver metastasis. These usually rather small series report 5-year survival rates of 25−50%. The study of the International Registry of Lung Metastases including 467 cases show a 5-year survival of 38%. So, in selected cases the adagium 'one course of surgical oncology results in a complete remission' may hold promise for a selected group of patients.

As in most primary breast cancers, also advanced breast cancer deserves multimodality treatment with appropriate systemic treatments and timely surgery and radiotherapy. Therefore, it is mandatory that patients with advanced breast cancer are discussed and treated within the multidisciplinary breast team, including the surgeon and radiation therapist.

207 Invited

Management of early metastatic breast cancer: brain metastases

W. Boogerd[1]. [1]*The Netherlands Cancer Institute, Neuro-Oncology, Amsterdam, The Netherlands*

Background: Brain metastases usually develop in patients with advanced metastatic disease. Whole brain radiotherapy is the standard treatment, that results in a median survival of 3−6 months, but half of the patients die of progressive systemic disease. In patients with brain metastases as only site of relapse outcome will be more dependent of the management of brain metastases.

Methods: Review of the literature and chart review of patients treated in the Netherlands Cancer Institute regarding incidence, risk factors, treatment and outcome of brain metastasis as first relapse of breast cancer.

Results: In about 20% of patients with brain metastases, the brain is the first site of relapse. Adjuvant systemic treatment is a risk factor for brain as first recurrence. Her2 overexpression, and use of trastuzumab as independent risk factors for brain as first recurrence are disputed. A solitary brain metastasis is a favourable prognostic factor. Treatment includes surgery, stereotactic radiosurgery, whole brain radiotherapy, but also systemic treatment. Neurosurgery and stereotactic radiosurgery of solitary brain metastasis provide the best tumour control with reported median progression free survival of one year or more. Recurrence of brain metastases is not uncommon: in selected cases re-resection or stereotactic radiosurgery affords local tumour control for 6−12 months in about 75% of cases; systemic chemotherapy may induce response or stabilisation in about half of those patients.

Conclusions: If the variety of therapeutic options including surgery, stereotactic radiosurgery, whole brain radiotherapy and systemic therapy is appropriately put into practice, prolonged and meaningful survival may be possible. However, the optimal combination and sequence of the different treatment modalities is not fully defined.

208 Proffered Paper Oral

Response to first line chemotherapy in BRCA1 and BRCA2 mutation carriers with metastatic breast cancer (MBC)

M. Kriege[1], C. Seynaeve[1], H. Meijers-Heijboer[2], J.M. Collee[2], M.B.E. Menke-Pluijmers[3], C.C.M. Bartels[3], A. van den Ouweland[2], M.J. Hooning[1], C.T.M. Brekelmans[1], J.G.M. Klijn[1]. [1]*ErasmusMC-Daniel den Hoed Cancer Center, Medical Oncology, Rotterdam, The Netherlands;* [2]*ErasmusMC, Clinical Genetics, Rotterdam, The Netherlands;* [3]*ErasmusMC-Daniel den Hoed Cancer Center, Surgery, Rotterdam, The Netherlands*

Background: Data of in vitro and small retrospective neo-adjuvant studies suggest that breast cancer (BC) (cells) without functional BRCA1 or BRCA2 protein have an increased sensitivity to chemotherapeutic agents causing double-strands DNA breaks, such as platinum and anthracyclin-containing regimens. In this study we compared the efficacy of first line chemotherapy in BRCA1- and BRCA2-associated MBC patients with that of sporadic MBC patients.

Patients and methods: We selected from the institutional database 112 BRCA1- and 29 BRCA2-associated patients, diagnosed with MBC before 2007, January 1. Patients were matched on year of birth, diagnosis primary tumor and diagnosis MBC (within 5 years periods) with 141 sporadic BC patients. Response rate (RR) on, progression-free survival (PFS) and overall survival (OS) after start of first line chemotherapy were compared between the 3 groups. Analyses were stratified for different chemotherapy regimens. Multivariate analyses were adjusted for estrogen receptor (ER)-status and adjuvant chemotherapy.

Results: As compared to sporadic patients, BRCA1-associated BC was more often ER-negative (78% vs. 42%; $P < 0.001$) and node-negative (57% vs. 37%; $P = 0.003$), and BRCA2-associated BC more often ER-positive (86% vs.58%; $P = 0.01$). First line chemotherapy consisted of anthracyclin-based regimens ($n = 147$), CMF ($n = 68$), taxane-based ($n = 21$) and other ($n = 6$) regimens. BRCA2-associated patients had a significant higher RR (89% vs. 50%; $P = 0.001$), a longer PFS (hazard ratio $(HR)_{multivariate}$ 0.64; $P = 0.04$) and a longer OS (HR_{mult} 0.53; $P = 0.005$) than sporadic patients. The longer PFS was especially observed for anthracyclin-based regimens (HR_{mult} 0.66) and disappeared for CMF (HR_{mult} 0.98). For BRCA1-associated MBC patients a non-significant trend for a higher RR (66% vs. 50%) and a longer PFS (HR_{mult} 0.79; $P = 0.14$) was observed. OS was not significantly different between BRCA1-associated and sporadic MBC patients (HR_{mult} 0.87).

Conclusion: Chemotherapy is more effective in BRCA2-associated MBC patients in comparison with sporadic BC patients, especially for anthracyclin-containing regimens. For BRCA1-associated MBC, a trend for a higher sensitivity to chemotherapy was observed.

209 Proffered Paper Oral

Trastuzumab plus docetaxel with or without capecitabine as first-line therapy for HER2-positive locally advanced or metastatic breast cancer: a randomised Phase II study

A. Wardley[1], A. Antón-Torres[2], X. Pivot[3], F. Morales-Vasquez[4], L. Zetina[5], M. de Fátima Dias Gaui[6], D. Otero Reyes[7], J. Jassem[8], P. Button[9], R. Bell[10]. [1]*Christie Hospital NHS Trust, Department of Medical Oncology, Manchester, United Kingdom;* [2]*Hospital Universitario Miguel Servet, Zaragoza, Spain;* [3]*University Hospital of Besançon, Besançon, France;* [4]*Instituto Nacional de Cancerología, Mexico City, Mexico;* [5]*Hospital Roosevelt, Guatemala City, Guatemala;* [6]*Instituto Nacional do Câncer, Rio de Janeiro, Brazil;* [7]*Hospital CIMA, San José, Costa Rica;* [8]*Medical University, Gdansk, Poland;* [9]*Roche Products Pty Ltd, Dee Why, Australia; 10. Andrew Love Cancer Centre, Geelong Hospital, Geelong, Australia*

Background: Trastuzumab (Herceptin®; H) + docetaxel (T) is standard first-line therapy for HER2-positive metastatic breast cancer (MBC). CHAT (Capecitabine, Herceptin And Taxotere), an international, open-label, randomised, Phase II study, evaluated the addition of capecitabine (Xeloda®; X) to the HT combination as first-line therapy for HER2-positive locally advanced breast cancer (LABC)/MBC.

Materials and Methods: Patients (pts) with HER2-positive (IHC 3+ and/or FISH+) LABC/MBC were randomised to receive H (8 mg/kg loading dose then 6 mg/kg q3w) + T (75 mg/m^2 in HTX arm and 100 mg/m^2 in HT arm, q3w) $\pm$ X (950 mg/m^2 bid on Days 1−14 q3w). The primary end point was overall response rate (ORR); secondary end points included duration of response (DoR), progression-free survival (PFS), time to progression (TTP), overall survival and safety.

Results: In total, 222 randomised pts received study medication. Baseline characteristics were generally well balanced. Median follow up for

the 2 arms was 25.5 (HTX) and 23.5 (HT) months. PFS and TTP favoured the HTX regimen (Table). Overall survival data are immature.

	HTX (n = 112)	HT (n = 110)	Hazard ratio	p value
ORR, %	71	73		0.72
Complete response, %	23	16		
Partial response, %	47	56		
Stable disease, %	25	16		
Progressive disease, %	4	9		
Median DoR, months	15.9	13.4		NC
Median PFS, months	17.9	12.8	0.72	0.04
Median TTP, months	18.6	13.6	0.70	0.03
1-year survival rates, % (95% CI)	91 (86, 96)	85 (79, 92)		
2-year survival rates, % (95% CI)	75 (66, 83)	66 (56, 75)		

NC, not calculated.

Most non-haematological adverse events (AEs) were grade 1 or 2. The most common grade 3/4 AEs were hand-foot syndrome (HTX 17%; HT <1%) and diarrhoea (HTX 11%; HT 4%). There was a lower incidence of grade 3/4 neutropenia in the HTX arm compared with HT (54% vs 77%). 12% of pts experienced mild to moderate cardiac AEs; 2 pts in each arm had left ventricular ejection fraction declines to <40%. Symptomatic congestive heart failure was experienced by 1 pt in each arm. No pt died due to a cardiac event. 4 deaths recorded during the study were considered to be treatment related (HTX 1 pt; HT 3 pts).

Conclusions: Both regimens demonstrated high ORR, with HTX achieving significant improvement in TTP and PFS compared with HT in HER2-positive LABC/MBC. Both treatments were manageable and cardiac safety was consistent with other H-based trials.

Thursday, 17 April 2008 16:00–17:30

CLINICAL SCIENCE SYMPOSIUM

Lifestyle and survival after treatment for breast cancer

210 Invited

What breast cancer survivors want to know about lifestyle after breast cancer

C. Murphy-Whyte[1]. [1]*Europa Donna Ireland, N/A, Co. Dublin, Ireland*

Awareness of cancer survival has increased greatly since the 1990's due largely to increasing numbers and the work of advocates. If prevalence of and survival with cancer worldwide continues to increase and follows predictions made in the USA, the number of recorded cancer survivors worldwide in 2025 will approach 50 million and in 2050 will approach 70 million. With a European prevalence rate of 34% for breast cancer – the most prevalent cancer in women – issues for breast cancer survivors will of necessity gain more attention.

From the point of diagnosis, breast cancer survivors have to deal with a confusing and disturbing array of conflicting studies and advice, reinforced by media hype regarding cancer scares and cures, so key issues for them are what and who to believe and where to find reliable evidence.

Most survivors will want to know the chances of their breast cancer progressing or recurring and what they can do to minimise those chances. Survivors are living longer and therefore long enough to develop new primary cancers or other chronic diseases.

Together with those who are closest to them, survivors want to learn about and act on helpful recommendations in terms of lifestyle based on sound evidence. They need recommendations on lifestyle that will not do them harm, that help limit the progress of breast cancer and help prevent a recurrence of breast cancer or any other cancer, and help prevent other diseases as well as improve the quality of their lives.

Studies and advice have traditionally focussed on significant components of lifestyle such as food, nutrition, and physical activity as applied to cancer risk and prevention and according to the WCRF/AICR report published in 2007, on the available evidence it is not yet possible to make judgements that apply specifically to survivors.

In tandem with the shift from life-threatening to life-changing disease, survivors want to know more about the changes that women are making in their lives following breast cancer. Apart from understanding more about maintaining a healthy immune system, survivors will increasingly want to extend the focus to address psycho-social aspects of lifestyle including working life, relationships, sexuality, the use of complementary therapies and supports and the complex interactions of stress and fatigue, on lifestyle choices. The challenge for advocates will increasingly be to find ways of getting these issues and appropriate methodologies onto the research agenda.

211 Invited

Stress, distress and support groups – are they important?

D. Kissane[1], B. Grabsch[2], D.M. Clarke[3], R.D. Snyder[4], Y. Li[1]. [1]*Memorial Sloan Kettering Cancer Center, Psychiatry & Behavioral Sciences, New York, USA;* [2]*University of Melbourne, Center for Palliative Care, Melbourne, Australia;* [3]*Monash University, Psychological Medicine, Melbourne, Australia;* [4]*St Vincent's Hospital, Medical Oncology, Melbourne, Australia*

Background: The sustained debate about group therapy and survival across the past decade distracted clinicians from the consistent evidence of quality of life benefits in reducing distress and depression when women with breast cancer attend support groups. A series of prospective, randomized, group therapy studies using larger cohort sizes failed to prolong survival in women with both metastatic (Canadian 235; Australian 227 and American 125) and early stage (Australian 303) breast cancer.

Material and Methods: DSM-IV diagnoses for psychiatric disorders and dimensional measures of anxiety, depression and quality of life were obtained in both Australian trials, where survival was the primary outcome; psychosocial well being was appraised secondarily.

Results: Anxiety was effectively relieved by group therapy in early breast cancer. Clinical depression was both actively ameliorated and new cases prevented across the course of the group therapy for advanced breast cancer compared to controls. Survival was not extended by either intervention.

Conclusions: These studies have consistently reduced distress and significantly prevented onset of new cases of depression in advanced breast cancer. The preponderance of systematic evidence supports the relief of distress, with the strongest evidence for anxiety-related outcomes (fear of recurrence) in early stage cancer. New evidence for the prophylactic benefit in preventing depression in advanced cancer argues for group support being offered to all interested subjects. Psycho-oncology needs to promote behaviors leading to health promotion (smoking cessation, obesity reduction and exercise), preventive screening and early detection, the relief of distress and culturally sensitive interventions to encourage adherence to anti-cancer treatments. Issues of medical mistrust and fatalism leading to anti-cancer treatment drop-outs could be addressed through these interventions.

212 Invited

Lifestyle interventions in breast cancer – what do we know and what do we need to know?

P.J. Goodwin[1]. [1]*Samuel Lunenfeld Research Institute at Mount Sinai Hospital University of Toronto, Medicine, Toronto, Ontario, Canada*

There is increasing recognition of the importance of lifestyle factors (e.g. obesity/body size, diet, physical activity) after breast cancer (BC) diagnosis. Over 50 studies have investigated obesity as a prognostic factor – the majority have identified an adverse prognostic effect. One meta-analysis identified a hazard ratio (HR) of 1.91 for distant recurrence and 1.60 for death for obese vs. non-obese women. Observational data have suggested that some dietary practices (e.g. increased intake of saturated fat in postmenopausal women) may increase risk of recurrence. Recent research has also suggested that low levels of physical activity around the time of BC diagnosis may also worsen prognosis.

Two randomized trials of lifestyle interventions have reported disease-free survival outcomes. The Women's Intervention Nutrition Study (WINS) studied the effect of reducing dietary fat intake to 20% of calories. Dietary fat reduction was associated with a relative weight loss of 2.3 kg. Five year relapse-free survival was significantly improved in the intervention arm (HR 0.76, p = 0.034). The effect was greatest in receptor negative (HR 0.58) vs. receptor positive (HR 0.85) BC. The Women's Healthy Eating and Living Study randomized women to a complex dietary intervention that involved fat reduction combined with increased intake of fruit, vegetables and fiber, up to four years post BC diagnosis. There was no effect on 5 year disease-free survival.

Intervention research (both randomized and non-randomized) has demonstrated the feasibility of physical activity after BC diagnosis. Improvements in fitness, quality of life and body composition have been demonstrated. There are no randomized trials of prognostic effects of physical activity. Similarly, the feasibility of weight loss through diet and physical activity has been demonstrated in BC patients. Apart from the WINS Study noted above, there are no randomized data addressing prognostic effects of weight loss.