improves the accuracy of noninvasive assessment of tumour dimensions. Ultrasound is the best predictor of size for axillary lymph nodes. Magnetic resonance imaging (MRI) is the most accurate imaging modality for the assessment of tumour response (size), the detection of multifocal or multicentric disease, and residual tumours after NC. Flattening of the contrast uptake time-intensity curve after the first chemotherapy cycle and complete absence of contrast uptake after the fourth cycle are observed in the responders. The patients with a concentric shrinkage pattern are good candidates for breast conserving surgery. H1 MR spectroscopy and nuclear imaging are very promising for identifying good responders early in the course of therapy (after one cycle). A low ratio of metabolic rate (18FDG-PET) relative to blood flow is a predictor of complete response. Nevertheless, all modalities are restricted in the imaging of very small residual tumour foci.

16 Proffered Paper Oral

Screening women with a familial or genetic predisposition to breast cancer: costs and effects of alternative screening policies

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Background: For the substantial proportion of women that have a more than average risk for breast cancer due to a familial or genetic predisposition, magnetic resonance imaging (MRI) is a promising screening tool. Estimates on breast cancer mortality reduction of screening these women are lacking, and randomized controlled trials are practically impossible.

Methods: In a prospective cohort study in 1952 women with increased breast cancer risk we estimated stage-specific sensitivity of different screening tests and resulting stage-shift by screen detection. Benefit of early detection was based on modeling estimates and pooled analyses of randomized mammography screening trials. We explored the effectiveness and cost-effectiveness of alternative screening policies for three cumulative lifetime (CLTR) risk categories: *BRCA1/2* mutation carriers (50–85% CLTR), a high-risk (30–50% CLTR) and a moderate-risk group (15–30% CLTR).

Results: Intensive surveillance including MRI in *BRCA1/2* mutation carriers is estimated to reduce breast cancer mortality by 50%, compared to 41% by mammography and clinical breast examination (CBE) only. Its effectiveness is almost twice as high compared to mammographic screening in women with population risk at 50. Screening *BRCA1/2* mutation carriers with biannual CBE and annual mammography and MRI from age 30 to 60 is at a cost of * 4314 per life-year gained (3% discounting). Offering MRI and mammography alternately at a 6 months interval is even more cost-effective. For the moderate-risk group, screening regimes with only mammography, alternating in combination with CBE, from age 40 to 50 years are most favorable in terms of cost-effectiveness (range * 3080–4764), and may lead to 25–31% breast cancer mortality reduction. Observed breast cancer incidence in the high-risk group did not differ substantially from the moderate-risk group. Waar zijn de low risks?

Conclusions: Addition of MRI in *BRCA1/2* mutation carrier surveillance is a very cost-effective screening policy, and should therefore be offered. For the moderate-risk category, intensive surveillance without MRI is defendable. Longer study follow-up is needed to advise a screening regime for the high-risk category.

Wednesday, 22 March 2006 14:15–16:00

SCIENTIFIC SESSION

How should we do phase II/III trials in the age of molecular biology?

17 Invited

When is a biological marker (or multimarker) ready to be tested in a clinical trial?

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Implementation of molecular biological parameters to test for therapy sensitivity may influence the way we are conducting clinical studies. So far the problem has been our limited knowledge about the mechanism controlling drug sensitivity in vivo. At this moment, only 2 predictive factors are used for therapy selection in breast cancer (BC); the estrogen receptor alpha (ER), and HER-2 amplification. Notably, these markers are also associated with breast cancer classification based on gene profiling in general [1], suggesting they both have a critical importance controlling tumor growth and behavior.

Yet while lack of ER and HER-2 expression signals non-responsiveness to hormonal manipulation and trastuzumab therapy respectively, patients expressing these parameters may still relapse despite optimal therapy, suggesting additional mechanisms of resistance to be involved. Considering chemoresistance in general, different attempts, including use of microarray techniques, have revealed gene profiles correlating to but not predictive of therapy responsiveness [2]. Considering individual markers, mutations in the TP53 gene as well as HER-2 amplifications have been associated with response to chemotoxics; however, none of these factors have revealed a sensitivity and predictivity sufficient for clinical implementations.

Clearly, there is a need for better predictive factors. The way forward probably lies in phase II neoadjuvant studies, in which proper tissue collection are made upfront and responsiveness to therapy carefully classified. There is actually little need to upfront hypothesize about individual predictive factors or array gene profiles predicting responsiveness. Assuming a time interval between editing a protocol and completion of patient data may last 3–5 years; most likely there will be a panel of novel potential predictive factors identified within that time interval. In this way, different phase II trials may identify and cross-validate the predictive value of individual as well as gene profile markers. Assuming resistance may be due not due disturbances in individual factors but rather disturbances in "functional pathways" [3], identification of certain markers may suggest other parameters involved up-/down-stream in the same pathways should be studied as well.

When is a parameter ready to be evaluated in a phase III study, selecting patients for individual therapy based on molecular profiling? This should mean some patients would be allocated to an experimental arm based on molecular testing and, as such, allocated away from standard therapy. In an ethical perspective however this is a decision not different from the ones we have been taking with respect to designing phase III trials in general; recent examples in breast cancer include trials evaluating aromatase inhibitors for adjuvant therapy. Thus, as soon we have sufficient evidence from phase II studies indicating expression of a particular marker may signal an experimental treatment approach to be advantageous, its clinical use should be confirmed in the phase III setting.

References

[1] Sorlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Nat Acad Sci 2001;98(19):10869–10874.

[2] Lønning PE, Sørlie T, Børresen-Dale A-L. Genomics in breast cancer – therapeutic implications? Nature Clin Pract Oncol 2005;2:26–33.

[3] Lønning PE. Genes causing inherited cancer as beacons identifying the mechanisms of chemoresistance. Trends Mol Med 2004;10:113–118.

18 Invited

Surrogate end-points: thick or thin ice?

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There is a long history of using surrogates in breast cancer research. For decades disease-free survival has been used as a surrogate for overall survival in studies assessing the efficacy of adjuvant treatment modalities