reconstruction should always be discussed as a treatment alternative. It should be emphasized that quality of life after 5 years is generally better after amputation as opposed to breast conservative therapy. If the risk of local recurrence exceeds 1% per year, which is the case in the very young, then mastectomy with reconstruction should be seriously considered as the method of choice. In particular in young breast cancer patients, unnecessary locoregional recurrence should be avoided and therefore optimal local therapy should be achieved.

37 INVITED

Having breast cancer at 29!

T. Chomiak-Salvi. *EUROPA DONNA European Breast Cancer Coalition, Milan, Italy*

I will take a personal approach to this presentation, describing the circumstances of my diagnosis and subsequent treatment. My story will introduce a few issues of concern to young women who are dealing with breast cancer: our relationships with our doctors and our expectations of them; our medical issues; the type of support we need during and following treatment. I was 29 years old in 1996 when I was diagnosed with breast cancer. I was at the beginning of a demanding career in the U.S. foreign service. I had been very healthy until my diagnosis, with no significant family history of cancer. Needless to say, I knew nobody who had been diagnosed with breast cancer at that age, nor did any of the doctors I saw at the time. Seven years later, I have not had any recurrences and I am once again very healthy. I have continued in my foreign service career, and I have begun a family. In the intervening years, I have made the disease my hobby, focusing especially on the ways it affects young women. I have observed what are young women's needs in dealing with breast cancer, and I have witnessed significant progress toward providing for those needs. My presentation is intended to open a discussion of those needs. My observations come from my experience in the U.S.A. However, I have lived and worked in Europe for a few years, including working on breast cancer issues, so I will make comments in a Transatlantic context.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Micrometastatic disease – what have we learnt?

38 INVITED

The nature of hypothetical micrometastases

M. Baum. *The Portland Hospital, Department of Oncology, London, UK*

Since the revolution in our thinking about the nature of breast cancer in the early 1970s we have inherited and codified a new set of dogma. These presume that the outcome of treatment is predetermined by the extent and growth characteristics of micrometastases present at the time of diagnosis.

To a significant degree these beliefs have been vindicated by the successes of conservative local therapy and adjuvant systemic regimens. However the time has arrived to challenge the new dogma, which fail to explain many clinical observations and the failure of screening and systemic cytotoxic treatment to fulfill their promise. The following observations have to be explained with a unifying hypothesis that can both incorporate the successes of the past and accommodate the failures:

- Anecdotal evidence of trauma provoking the outgrowth of distant metastases.
- Failure of local control has a significant impact on survival after all.
- Distant metastases are rare at the time of presentation yet within three years their rate of appearance is proportionate to the size of the tumour at diagnosis.
- There is not a constant hazard rate for recurrence over time but a steep peak at three years.
- The results of adjuvant chemotherapy and high dose chemotherapy in particular are very disappointing.
- There is an ***increase*** in breast cancer mortality in the early years of screening for the premenopausal women.
- The point in the menstrual cycle at which a young woman is treated may have an influence on outcome.

I propose that screen detected DCIS or the micrometastases in the established disease are ***not*** in an active state of proliferation but in a state of dynamic equilibrium that can be perturbed by the very act of diagnosis of latent pathology or the surgery for the established disease [1]. To explain these phenomena one has to invoke the mathematics of complex systems (chaos theory) and reject simplistic notions of logarithmic or Gompertzian growth.

The accumulated evidence to support this contention was recently reviewed in *Lancet Oncology* [2].

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39 INVITED

Micrometastases in bone marrow

M. Osborne. *The Strang Cancer Prevention Clinic, New York, USA*

The majority of patients with breast cancer present with Stage I or II disease; approximately one third relapse at distant sites and subsequently die of the disease. Distant metastases occur because local-regional disease sheds tumor cells into the blood circulation. Some of these tumor cells are capable of the multistep process of establishing micrometastatic, and subsequent clinically apparent, disease. Currently the key prognostic factors predicting distant metastatic disease and survival are the maximum tumor diameter, the presence of lymph node metastases and, in lymph node negative patients, tumor histologic or nuclear grade and/or the presence of peritumoral lymphovascular invasion.

Studies carried out since the late 1970's have consistently shown bone marrow micrometastases (BMM) to be present in 25–35% of patients at the time of initial surgery [1–5]. These studies have also shown that the presence of BMM correlates with short term increased distant relapse rates and reduced survival [2–7]. The presence of BMM has, in some studies, been shown to be an independent prognostic factor [8] and, in one study, the strongest single predictor of prognosis [5]. BMM do not predict for site of relapse but appear to be a biological marker for relapse at any site.

One long-term study showed that BMM did not independently predict relapse or survival [1]. We used a different statistical model for non-proportional data and with 15 years of follow up showed that BMM was an independent prognostic factor [9]. Further long-term confirmatory studies are required to determine the value of BMM as a long-term prognostic factor. The ACOSOG Z-10 trial is currently evaluating the prognostic value of bone marrow aspiration carried out at the time of initial surgery.

Cytokeratin positive cells in the bone marrow have been shown to be rarely proliferating, based on studies using Ki-67, and there was no reduction in BMM after adjuvant chemotherapy suggesting that non-proliferating, dormant cells may not be susceptible to chemotherapy [10]. Persistence of BMM after adjuvant chemotherapy indicates a poor prognosis [11].

Bone marrow micrometastases can be detected by immunofluorescence [2], immunocytochemistry [12] and polymerase chain reaction (PCR) [13]. Sensitivity studies in a model system using immunocytochemistry have shown that one cancer cell can be detected in one million normal bone marrow cells [12]. The molecular detection of cancer cells in bone marrow can be accomplished by amplifying DNA or mRNA of malignant cells using rtPCR, which may detect one tumor cell in up to 10 million normal cells [13]. However, this technique may be overly sensitive and difficult to quantify.

In conclusion, the presence of bone marrow micrometastases is an independent prognostic indicator of early relapse and survival and may also indicate long-term prognosis. The role of sequential detection of BMM to monitor adjuvant chemotherapy needs further study. Long-term studies are required to evaluate the utility of BMM detection and the molecular features of the primary tumor associated with BMM [14].

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40 INVITED

Micrometastases in axillary sentinel lymph nodes of breast carcinoma patients

G. Viale[1,2]. [1]*European Institute of Oncology, Department of Pathology, Milan, Italy;* [2]*University of Milan, School of Medicine, Milan, Italy*

The very high negative predictive value of axillary sentinel lymph node (SLN) biopsy in staging patients with clinically node-negative breast carcinoma allows almost 65–70% patients to be spared axillary lymph node dissection (ALND) and its associated morbidity because of a metastasis-free SLN. Conversely, in case of a positive SLN biopsy, the standard of care remains completion ALND for a more exhaustive staging. Further axillary involvement, however, will not be identified in the majority of these patients, who will not derive any benefit from axillary dissection. Thus, a predicted small chance of additional axillary metastasis after a positive SLN biopsy might justify avoiding ALND also in a selected cohort of patients with positive SLN biopsy.

The size of SLN metastasis has emerged as a most powerful independent predictor. In particular, patients with micrometastatic SLN (i.e. SLN harboring metastases up to 2 mm in maximum diameter) reportedly are at a significantly lower risk for further axillary involvement than patients with SLN metastases larger than 2 mm (13–24% *vs* 45–79%). The new edition of the TNM classification of malignant tumors has now separately classified patients with isolated tumor cells (ITC) only in the regional lymph nodes within the pN0 (i+) category, and it remains to be determined whether it is meaningful and can be safely adopted also for staging patients undergoing SLN biopsy. In particular, the question now arises whether or not patients with breast carcinoma and ITC only in the axillary SLN are at such a low risk for additional nonsentinel lymph node metastases that completion ALND may not be necessary.

Methods: All the axillary sentinel and nonsentinel lymph nodes of 1228 patients were reviewed histologically, and reclassified according to the current TNM classification of malignant tumors, as bearing isolated tumor cells only, micrometastases or (macro)metastases. The prevalence of metastases in nonsentinel nodes was correlated to the type of SLN involvement and the size of the metastasis, the number of affected SLNs, and the prospectively collected clinicopathologic variables of the primary tumors.

Results: In multivariate analysis, further axillary involvement was significantly associated with the type and size of SLN metastases, the number of affected SLNs, and the occurrence of peritumoral vascular invasion in the primary tumor. A predictive model based on the characteristics most strongly associated with nonsentinel node metastases was able to identify subgroups of patients at significantly different risk for further axillary involvement.

Conclusions: Patients with the most favorable combination of predictive factors still have no less than 13% risk for nonsentinel node metastases and should be offered completion ALND outside of clinical trials of SLN biopsy without back-up axillary clearing.

41 INVITED

Micrometastatic cells as targets for adjuvant therapies

K. Pantel. *Universitätsklinikum Hamburg-Eppendorf, Institute für Tumorbiologie, Hamburg, Germany*

Using monoclonal antibodies to epithelial cytokeratins (CK), individual carcinoma cells can be detected on cytologic preparations at frequencies of 10^{-5} to 10^{-6} (for review, see Pantel et al., Clin. Cancer Res., 2003). Several prospective clinical studies have shown that the presence of CK-positive cells in bone marrow of patients without clinical signs of metastases is prognostically relevant (e.g., Pantel et al., Lancet, 1996; Braun et al., NEJM, 2000; Wiedswang et al., JCO, 2003). In addition to immunocytochemistry, new molecular detection methods based on the amplification of a marker mRNA species by the polymerase chain reaction technique have been developed.

The current assays may be used to improve tumor staging with potential consequences for adjuvant therapy. Another promising clinical application is monitoring the response of micrometastatic cells to adjuvant therapies, which, at present, can only be assessed retrospectively after an extended period of clinical follow-up. In particular for therapeutic monitoring, the analysis of peripheral blood samples is more feasible than the repeated sampling of bone marrow. Several new reliable blood tests are now available and the clinical data obtained with these assays look very promising.

Another important goal is to unravel the biology of the onset of metastasis and search for new therapeutic targets on micrometastatic cells. Our recent expression profiling investigation indicated that hematogeneous micrometastasis in breast cancer is associated with a specific molecular signature of the primary tumor (Woelfle et al., Cancer Res., 2003). The direct analysis of micrometastatic cells in blood and bone marrow is hampered by the low concentration of these cells. The tools established in our laboratory (e.g., micrometastatic cell lines, single cell (RT)PCR, multiple labeling, and FISH) allow to obtain further insights into the phenotype and genotype of single micrometastatic cells. The available data indicate that micrometastatic cells represent a selected population of cancer cells which, however, still express a considerable degree of heterogeneity with regard to chromosomal aberrations and phenotypic properties (Solakoglu et al., PNAS, 2002; Kraus et al., GCC, 2003). Prominent characteristics of micrometastatic cells in blood and bone marrow at the time of primary tumor diagnosis are the lack of proliferation-associated marker proteins (Pantel et al., JNCI, 1993, Offner et al., PNAS, 1999), which may limit the efficacy of adjuvant chemotherapy (Braun et al., JCO, 2000). On the other hand, the frequent expression of the HER2/neu oncogene supports the idea that antibodies or inhibitors directed against this receptor may be useful drugs to eliminate micrometastatic cells (Pantel et al., JNCI, 1993 & 1999; Putz et al., Cancer Res., 1999; Braun et al., Cancer Res., 2001). Interestingly, MHC class I antigens were frequently downregulated (Pantel et al., Cancer Res., 1991), which may limit immunotherapies based on active vaccination against residual tumor cells.

In conclusion, the detection and characterization of micrometastatic cells may improve tumor staging and helps to design new adjuvant therapies to eliminate minimal residual cancer in patients with solid tumors.

Wednesday, 17 March 2004 14:15–15:45

SYMPOSIUM

Psychology and breast cancer: state of the art

42 INVITED

Psychological comorbidity in breast cancer patients

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The diagnosis and treatment of breast cancer results in various sequelae in the affected women which can have a considerably negative effect on their quality of life. These include emotional destabilization, an alteration of the physical integrity and self perception, uncertainty regarding social roles and responsibilities, and a modified interactional relationship to their environment.

The present lecture focuses on the issue of psychological comorbidity in breast cancer patients. The relevance of this topic is indicated by evidence which suggests that patients with an additional psychological disorders have a higher risk of morbidity and mortality, a higher risk of chronification