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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