92

GENETIC AND PHYSIOLOGIC CONSIDERATIONS IN RADIOTHERAPY OF BREAST CANCER. Dvořák,E., Vincennes Cancer Treatment Center, Good Samaritan Hospital, Vincennes, Indiana, U.S.A.

Correct definition of breast carcinoma has a direct impact on its treatment and prognosis. Physiologically, breast belongs to the reproductive system. It is therefore a systematic disease, but not a priori systemic, i.e. with widespread subclinical metastases. As with any cancer, it is a genetic disease due to DNA sequence alteration; in addition, it appears to be of autosomal dominant inheritance, obeying the laws of population genetics with a frequency of susceptibility allele p=0.056-0.065. Homozygotes with a frequency of p^2=0.003-0.004 may represent cases with a near-complete penetrance while heterozygotes (2pq=0.10-0.12) would mostly correspond to usually presumed phenocopies and/or new mutations. Since population frequency of breast carcinoma, based on the lifetime risk in women, is 0.11-0.12, all breast cancers may be inherited traits with varying penetrance. Efferent lymphatic vessel invasion appears as a grave pathophysiologic element in distant spread, in case of internal mammary nodes probably enhanced by subatmospheric intrathoracic pressure. Adequate locoregional treatment in early breast carcinoma should be reassessed as a potential factor of improved survival.

94

BREAST CARCINOMA : THE PROGNOSTIC RELEVANCE OF ER.R FACTOR IN ASSOCIATION WITH pS2 AND c-erbB-2 STATUS. Gotteland M.[1], May E.[1], May-Levin F.[2], Contesso G.[2], Delarue J.C.[2], and Mouriesse H.[2]. [1]IRSC, Laboratory of Molecular Oncology, [2]Institut Gustave-Roussy - Villejuif - France.

The response to endocrine therapy is not entirely predictable from the oestrogen receptor (ER) and progesterone receptor (PgR) status of primary breast tumours. We previously proposed a new prognostic factor, ER.R, which was based on both ER-protein and ER-mRNA levels. A previous analysis of 88 primary breast carcinomas showed that ER.R permits the identification of a subset of ER+ women presenting a higher risk of early relapse (Oncogene 1989; 4:1037-42). Results presented here confirmed this first observation by analysing a larger number of patients.

ER-protein levels were determined for 171 primary breast cancers either by radioligand binding assay (ER-LBA) or by enzyme immunoassay (ER-EIA). ER-, pS2- and c-erbB-2-mRNA were measured by Northern blot.

ER.R factor is determined by calculating the ratio values [ER-protein in fmol / mg total proteins] to [ER-mRNA in pg / 4mg total RNA]. A cut-off value of 1.5 (protein levels measured by ER-LBA) or 3 (protein levels measured by ER-EIA) discriminate the two ER.R1 (lower ratio) and ER.R2 (higher ratio) subgroups that present a significantly lower and higher risk of early relapse, respectively. No association was found between ER.R status and either PgR status or c-erbB-2 and pS2 expression. According to a Cox multivariate analysis for disease-free survival, the two stronger factors in predicting a poor prognosis were c-erbB-2 overexpression and ER.R2. In the present analysis ER.R2 was ahead of ER negativity as predictor of recurrence.

In accordance with our first published data, analysis of a larger population with a longer follow-up showed that ER.R keeps its significance to predict outcome of patient, whatever assay was used to quantified ER.

96

TREATMENT OF METASTATIC BREAST CANCER WITH TRIPLE M CHEMOTHERAPY

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At the Department of Obstetrics and Gynaecology, University of Erlangen, 61 patients with metastatic breast cancer were treated between 1989 and 1992 with a combined chemotherapy of mitomycin, mitoxantrone and methotrexat.

In the case of metastases patients received 8 mg/m^2 mitoxantrone and 30 mg/m^2 methotrexat every 21st day and 8 mg/m^2 mitomycin every 42nd day for at least 6 cycles.

Patients belonged to a high risc group with a median age of 52 years, 52% premenopausal women, 60% receptor negative patients and a relapse free intervall of less than 2 years in 59% of the patiens.

As objective side effects were leukocytopenia and thrombocytopenia observed but only 8% had a serious leukocytopenia which needed special treatment and 3% of the patients suffered from a severe thrombocytopenia.

The responds rate was 69% with a median remission time of 7 months.

As a resume we found that Triple M is an effective combined chemotherapy in the treatment of the metastatic breast cancer with acceptable side effect.

93

WHAT IS THE RISK OF INVASIVE TUMOR IN LCIS OF THE BREAST?

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One hundred and fifty-seven women, 25 with family history of breast cancer, mean age 48 years (range 27-72), 49 (31%) pre and 108 (69%) post-menopausal, underwent surgery for palpable or mammographically detected breast lesions: 153 (97.5%) received local excision and 4 mastectomies. Histology excluded invasive cancer, but one or more foci of in situ lobular carcinoma (LCIS) were observed in each excised specimen. Following this fortuitous diagnosis of LCIS 37 patients were radicalized, 35 by quadrantectomy and 2 by mastectomy, and 120 received no further treatment. Most cases were followed regularly but 1 was lost to follow-up. There have been no recurrences in the 6 women who underwent total mastectomy. In the conservatively treated and followed patients (mean duration 66 months), 8 (4 multifocal and 4 unifocal primaries) presented another LCIS at a mean distance of 52 months (range 12-142) from the first LCIS diagnosis; all were again treated conservatively. Five cases (3.2%) developed a homolateral infiltrating carcinoma (2 lobular and 3 ductal) at a mean distance of 49 months (range 15-87). In the controlateral breast 2 patients (1.3%) developed in situ lobular carcinoma and 5 infiltrating ductal carcinoma. The risk of women presenting with homolateral invasive cancer after diagnosis and conservative treatment of LCIS was calculated comparing breast cancer incidence in these women with expected breast cancer incidence in the female population of the same age for the period 1978-1981. By the person/year method the rate/1000/year (observed/expected) is 5.34. It is concluded none-the-less that this risk (5.3 times higher than the general population) does not indicate the use of mutilating procedures such as total mastectomy. A wait and see policy seems more appropriate.

95

TUMOR CELL KINETICS AND TUMOR VASCULATURE IN BREAST CANCER.

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To assess the intratumor variability in cell kinetics and the relationship with tumor vasculature, we studied 48 patients with breast cancer (32 IDA, 9 ILA, 6 mixed IDA/ILA and 1 colloid carcinoma). Primary treatment was surgery. Following preoperative IUdR injection, potential doubling time (Tpot) was measured in a total of 205 biopsies (3 to 5 per tumor). Tumor vasculature was assessed on fresh frozen tissue using immunohisto-chemistry and image analysis.

Mean Tpot was 29.69 ± 23.42 days. Intertumor variability largely exceeded intratumor variability (analysis of variance (ANOVA): $F = 8.5$, $p < 0.0001$). Diploid tumors were significantly slower proliferating than aneuploid tumors (mean Tpot 42.1 vs. 21.5 days). Within the aneuploid subgroup, ILA were significantly slower proliferating than IDA (ANOVA: $F = 27.8$, $p < 0.0001$), and vascular density increased significantly with T stage (ANOVA: $F = 4.4$, $p < 0.05$). There was no correlation between T stage and mean vascular diameter. Tpot did not correlate with vascular density nor with mean vascular diameter.

In conclusion, Tpot can be measured reliably in aneuploid breast tumors. In our study, tumor size at time of diagnosis correlated with vascular density, although not with proliferation rate.

97

RADIAL SCARS - A SCREEN-DETECTED LESION THAT MUST BE REMOVED

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With the introduction of the National Screening Programme, the incidence of radial scars (RS) has dramatically increased. Opinions are divided regarding the significance of these lesions and their relationships to underlying cancer. This study categorizes RS into two types:floret-like (small < 6 mm) and irregular (large 3-20 mm), and relates their presence to neoplastic change.

82 RS were removed in a three year period. In 15 patients this was an incidental finding after breast tissue was removed for a cancer, and 11 of these were floret-type. The remaining 67 RS presented as a mammographic or clinical abnormality and 84% of these were the irregular type. 34 of these true RS were associated with benign breast disease. However 23 had associated invasive (16) or non-invasive (7) cancers and 10 had atypical ductal hyperplasia. Stereotactic cytology and mammography were unhelpful in predicting neoplastic change.

All screen-detected RS should be removed. It is suggested that this becomes a Quality Assurance guideline.