MONDAY 15 SEPTEMBER 1997

Symposia

286

Breast cancer predisposition genes

D.M. Black, F. Harris, A. Renwick. *Beatson Institute for Cancer Research, Switchback Road, G61 1BD Glasgow, UK*

Greater than 10% of breast cancer cases are attributable to mutations in susceptibility genes. *BRCA*1 and 2 mutations are rare, with population frequencies of between 0.002 and 0.001. However, these genes are associated with a particularly high risk of breast cancer, each having mutant alleles with greater than 80% penetrance. The *BRCA*1 and 2 genes account for the vast majority of families with multiple cases of breast cancer. Mutation carriers are also at increased risk of other malignancies. Loss of function *BRCA*1 and 2 susceptibility mutations have been identified in many families, allowing for the presymptomatic screening of potential carriers. As these are large genes, screening using conventional techniques is both labour intensive and expensive. However, certain populations have been characterised in which the same *BRCA*1 and 2 mutations are present in multiple families. These are usually associated with a common haplotype for flanking genetic markers, indicating that they result from an ancestral mutation. The most notable examples being the 185delAG *BRCA*1 and the 6174delT *BRCA*2 mutations, each of which are present in the Ashkenazi Jewish population at a frequency of greater than 1%. Screening for the common mutations is quick and relatively inexpensive. It is believed that other low penetrance genes may account for a greater proportion of breast cancer cases than those attributable to *BRCA*1 and 2. One such gene is *ATM*, which has a carrier frequency of about 1 in 200. It has been estimated that *ATM* carriers have a 4-fold increased risk of breast cancer, compared to non-carriers. It is therefore possible that 5% of all breast cancer cases are due to *ATM* susceptibility mutations.

287

Molecular and biologic markers of DCIS, ADH and IDC

Sylvie Ménard. *Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy*

Purpose: Infiltrating ductal breast carcinomas (IDC) originate from presumed in situ precursor lesions. Recently, atypical ductal hyperplasia (ADH) was shown to derive from a monoclonal proliferation and can therefore be considered a neoplasic precursor lesion of IDC. Ductal carcinoma in situ (DCIS) might be an intermediate step in the transformation process between ADH and IDC or, alternatively, ADH might represent a direct precursor of some IDC.

Methods: The biological and molecular characterisation of the different lesions help answering this question.

Results: ADH are negative for c-erbB-2 overexpression, whereas 70% of DCIS (mainly the comedo type) and 30% of IDC are positive for overexpression of this oncogene. If DCIS were the precursor lesion of all IDC, this would imply a decrease in c-erbB-2 overexpression during transformation from DCIS to IDC, which is very unlikely considering the definitively established role of this oncogene in tumour progression. Thus, it is possible that a proportion of IDC, mainly those that are negative for c-erbB-2 overexpression, derive directly from ADH or from non-comedo type DCIS. This possibility is consistent with the observation that most of the pathobiologic parameters found in comedo type DCIS, such as high grade, necrosis, lymphoid infiltration, c-erbB-2 overexpression and p53 alteration, are also found in some but not all IDC, supporting the concept that two different in situ lesions give rise to two different IDC. Indeed, our multiple correspondence analysis of 700 primary IDC revealed an association between different DCIS-related characteristics, which when used together, delineate two subsets of IDC. These two subsets were found to differ with respect to age at diagnosis, prognosis, time to recurrence and response to therapy.

Conclusions: Together, these data suggest that IDC comprises two different diseases that can be identified based on pathobiologic characteristics and that derive from two different preinvasive precursor lesions.

288

Genetic alterations in ductal carcinoma in situ of the breast: Association with histologic type

M.J. van de Vijver[1,2], J.L. Peterse[1], C. Vos[2], N. ter Haar[2]. [1]*Dept. of Pathology, Netherlands Cancer Institute, Amsterdam;* [2]*Leiden University Hospital, Leiden, Netherlands*

Purpose: Ductal carcinoma in situ (DCIS) of the breast is heterogeneous with respect to histologic and clinical characteristics. Recently, a histologic classification of DCIS has been proposed: poorly differentiated, intermediate and well differentiated DCIS (Holland et al., Sem. Diagn. Pathol. 11: 167–180 (1994)). We have characterized the profile of genetic alterations in DCIS in relation to histologic type.

Methods: 164 Cases of DCIS and 9 cases of lobular carcinoma in situ (LCIS) were collected. Immunohistochemical staining was done using various antibodies, DNA isolated from frozen material and from paraffin was analyzed for gene amplification and loss of heterozygosity (LOH).

Results: c-erbB-2/neu and cyclin D1 gene amplification and protein overexpression, p53 overexpression and LOH on chromosome 17 were associated with intermediate and poorly differentiated DCIS; LOH on chromosome 16 was associated with well differentiated DCIS. E-cadherin inactivation was found in all cases of LCIS, but never in DCIS.

Conclusion: Each of the different histologic types of DCIS is associated with specific genetic alterations.

289

The surgical management of screening detected and genetic breast cancer

L. Holmberg. *Department of Surgery, University Hospital, SE-751 85 Uppsala, Sweden*

There are so far no prognostic markers to tell us that screening detected or genetic breast cancer should be treated widely different from lesions detected clinically. Thus the overriding principles for surgical treatment is the same in these clinical domains, namely radical excision of the primary tumour and adequate staging with due consideration of functional and cosmetic results.

However, there are some important qualifications. A quality assurance goal for mammography screening within EU is that the proportion of invasive cancer less than 15 mm in diameter should be at a minimum of 50% of the invasive cancers detected at screening. A large proportion of these cancers will have a low malignancy grade at the risk of finding axillary metastases at an axillary dissection will be small. Of malignant lesions overall detected in a screening program, 15–20% will be DCIS. In both these patient groups surgeons are confronted with the challenge to both ensure that small palpable or non-palpable lesions have been securely removed and avoid overtreatment both in terms of the amount of breast tissue resected and how the axilla is explored. The sentinel node biopsy technique for the axilla is a most welcome development.

For hereditary breast cancer the management of the contralateral breast presents a clinical dilemma. A search for indicators – such as e.g. the patient's family history, type of tumour and age at diagnosis – for choice of surgical management of the contralateral breast is important.

290

Update on ductal carcinoma in situ trials

J.P. Julien, C. Henri. *E.O.R.T.C. Breast Group; Becquerel Rouen FR, France*

It is tough to carry out a clinical trial for the treatment of slow growing lesions which criteria constantly change and for which many aspects are still unknown. Therefore trials activated often more than ten years ago included all D.C.I.S, the classification was based on architectural pattern

and borderline lesions, Atypical Hyperplasia, Micro Invasion had marked interobserver variations. During the eighties with the increase in detection of D.C.I.S., several trials were activated in Europe and United States. In order to find the optimal management mainly to develop like in invasive cancer conservative surgical procedures and to appreciate the role of radiotherapy. 3 trials activated separately in Germany, Denmark and Norway end up by lack of accrual. A Swedish one is still on the way. 2 others trials evaluate the worth of radiotherapy and also Tamoxifen: The U.K. D.C.I.S. trial still open and the N.S.A.B.P. B24 closed. E.O.R.T.C. in Europe and N.S.A.B.P. in the United States performed two identical trials: Wide complete excision with or without Radiotherapy (50 Gy). The N.S.A.B.P. B17 has been closed in December 1990 with 818 patients. Results have been published at 5 and 8 years of Follow Up. Disease Free Survival: Surgery = 72% and 62% – Surgery + Radiotherapy = 83% and 75% (P: 0.00003). But overall survival at 8 years is 94% and 95% (N.S.). At 8 years the cumulative incidence of local invasive recurrence decrease from 13.4% to 3.9% and for non-invasive from 13.4% to 8.2%. The E.O.R.T.C. is closed since 7/96 with 1010 cases. No data by treatment arm are yet available but the whole population D.F.S at five years is 79% and invasive D.F.S survival is 90%. In both trials, the average incidence rate of local recurrence during the first five years is about 4%.

291

Genes and the development of prostate cancer

N.J. Maitland. *YCRC Cancer Research Unit, Dept of Biology, Univ of York, York YO1 5DD, United Kingdom*

Human prostate cancer is a complex disease whose clinical outcome is frequently difficult to predict by traditional histopathological and clinical diagnostic techniques such as serum PSA testing. In particular, the degree and severity of metastatic spread has posed problems in terms of management of disease. It is clear that there is a genetic component in prostate cancer with possibly significant differences between the familial form, which is relatively rare and affects younger patients in the 40–60 age group, and the sporadic form which affects most elderly patients. The advent of the "new genetics" and high throughput screening of patients can narrow down and identify first of all gene loci and then genes themselves and should bring untold benefits to the fields of both diagnosis and treatment.

While no novel genes directly predisposing to prostate cancer have yet been isolated, a number of promising loci have been identified on human chromosome 1 for familial prostate cancer and most notably in chromosomes 8, 10 and 16 for sporadic prostate cancers. Genetic analysis of single tumour foci from individual patients using polymorphic microsatellite probes indicates that prostate cancer is as complex genetically as it appears clinically in terms of responses to therapy.

The significance of these gene loci will be discussed and their potential for application in new and more effective treatments, including the development of gene therapy directed into the prostate will also be described.

292

Screening programmes for prostate cancer. Is it worthwhile?

J. Weyler, M. Matthyssen. *Department of Epidemiology, University of Antwerp, Belgium*

Where the application of early diagnosis and screening seems to be driven by 'common sense', there are unfortunately only a few situations in which there are more advantages than drawbacks. Therefore, a number of conditions have to be met in order to decide the implementation of this approach for a specific disease. At this moment there seems not to be an indication that for the case of prostate cancer these premises are met.

Prostate cancer is mainly a problem in the elderly and as such rather to be described as a frequent cause of death than as a major health problem. In Western Europe, men dying from prostate cancer have a better life expectancy than the mean new-born. More men seem to die with prostate cancer than as a result of it. Unfortunately, at the moment of (early) diagnosis it is not possible to make a clear distinction between aggressive and non-aggressive malignant tumours. Even on the assumption that this major problem would not exist and that the targeted illnesses would be all histologically proven malignancies, an other problem arises. The existing methods for early diagnosis of prostate cancer (digital examination, PS and trans rectal ultrasonography), lack the validity required for implementation in general populations. Application of Bayes' theorem indicates that the predictive values of the different tests are disappointing when applied in the (low prevalence) general population. Moreover, in the asymptomatic population stage distribution is centred to the early stages which are more difficult to detect leading to a decrease of the overall sensitivity.

Although it is clear that the implementation of prostate cancer screening might elucidate on the natural history of disease and some of the aggressive tumours might be detected, the negative effects are unacceptable. Over diagnosis and over treatment will be a major problem. Moreover it is still not very clear at this moment whether the treatment of prostate cancer is beneficial in the first place. It seems therefore that for the time being screening for prostate cancer should be discouraged.

294

Adjuvant hormonal therapy in locally advanced prostate cancer treated by external irradiation

M. Bolla. *On behalf the EORTC Radiotherapy Group; Cancérologie-Radiotherapie, BP 217, France*

Regional disease is represented by stages T2c-T3-4 N0 M0, or T1c-4 N1-3 M0, and is usually treated by external irradiation and or hormonotherapy. The long term results of external irradiation as regards survival and progression free survival are progressively decreasing and the higher the clinical stage, the poorer the prognosis. Prostate cancer is an hormonodependant cancer: we can assume that hormonotherapy may act inside and outside the planning target volume by helping to inhibit repopulation during irradiation and destroying hormone dependent micro-metastases. By combining hormonotherapy – LHRH analogue ± antiandrogen – with external irradiation before and during, or during and after irradiation, it is now possible to improve survival.

The Radiation Therapy Oncology Group has previously reported two randomized studies which have addressed the role of a short term hormonotherapy delivered before and during external irradiation (protocol 86-10) and the role of a long term hormonotherapy given after external irradiation (protocol 85-31). In protocol 86-10 including patients with large T2, T3, T4 tumors, hormonotherapy was initiated 2 months prior starting radiotherapy and terminated at the completion of radiotherapy, and resulted in a significant improvement of prostatic local control ($P < 0.001$), incidence of distant metastases ($P < 0.001$), progression free survival ($P < 0.001$). As to protocol 85-31, adjuvant hormonotherapy with goserilin started at the end of radiotherapy and continued indefinitely, obtained the same results: decrease of local failure ($P < 0.001$), distant metastases ($P < 0.001$) and progression-free survival ($P < 0.001$). In EORTC protocol 22863 immediate hormonotherapy (Goserilin, Zoladex, 3.6 mg s. c. every 4 weeks) was compared to deferred hormonotherapy. Hormonotherapy started on the first day of irradiation and continued for 3 years., resulted with a median follow-up of 45 months., in an increase of 5-year local control from 77 to 97% ($P < 0.001$), clinical disease-free survival from 36 to 74% ($P < 0.001$), and overall survival from 62% to 79% ($P < 0.001$).

295

Conformal radiotherapy of prostate cancer

J.V. Lebesque. *Department of Radiotherapy, The Netherlands Cancer Institute/Antoni van Leeuwenhoek Huis, Amsterdam, The Netherlands*

Since conventional radiotherapeutic treatment of prostate cancer is associated with a relatively high frequency of local relapses, three-dimensional conformal radiotherapy (3D-CRT) is being developed to optimize local control. The principle of 3D-CRT is that by conforming the treated volume to the target volume, the amount of irradiated normal tissue can be reduced, such that dose-escalation may be allowed without increasing the risk on normal tissue complications. Since 3D-CRT involves tight margins around the Clinical Target Volume (CTV), geometrical accuracy is a prerequisite for 3D-CRT.

The positional uncertainty of the CTV during treatment is determined by organ motion within the patient and patient setup deviations. Prostate motion has been quantified by performing repeat CT scans during treatment and could be described by rotations around the left-right axis with the apex of the prostate as centre of rotation. The random component due to daily differences in rectal filling was equal to 4 degrees (1 SD). The systematic component was caused by more rectal filling during the planning CT scan compared with the average degree of rectal filling during treatment. This component was reduced by repeating the planning CT scan in case of large rectal filling. Translational and rotational patient setup deviations have been measured by portal imaging. The random components due to daily setup deviations were equal to 1.8 mm (1 SD) and 0.7 degree (1 SD). The number of mean 3-D deviations larger than 4 mm could be reduced from 37% to 5% by applying a setup verification and correction procedure.

Using 3D-CRT with tight treatment margins, a dose escalation study has been performed, indicating that a total dose up to 78 Gy is feasible without increasing rectum and bladder complications.