21

PREDICTIVE ASSAYS IN RADIOTHERAPY

Streffer C, Institute for Medical Radiobiology, University Clinics, Essen, Germany

Studies of biological parameters on human tumors have shown a high heterogeneity between individual tumors even if tumors of the same clinical stage and histopathological grading have been studied. It is assumed that this heterogeneity contributes largely to the variability of tumor response to therapy. Therefore it appears necessary to determine such biological parameters which are relevant for a therapeutic response in order to optimize tumor therapy on an individual basis. Radiobiological data have demonstrated that the following parameters and processes are important for the therapeutic response:

- Intrinsic cellular radiosensitivity
- Efficiency of DNA repair
- Cell proliferation and repopulation of tumor cells
- Oxygen supply in the tumor tissue
- Metabolism, microenvironment within the tumor

Many efforts have been undertaken to develop simple tests in order to determine these parameters in individual tumors and to correlate the data with the outcome of the clinical treatment.

Thus it has been observed that the survival fraction of cells varies appreciably after 2 Gy irradiation. A number of predictive assays has been developed on the basis of measuring the clonogenicity of tumor cells and the results have been compared with the clinical outcome. These tests are very time consuming therefore a simple test system the micronucleus assay has been introduced in order to measure intrinsic radiosensitivity. It has been shown successfully with several tumor entities.

Cell proliferation and repopulation of tumor cells plays a significant role for the development of local recurrences after radiotherapy. Several flow cytometry methods have been worked out in order to measure these parameters. DNA measurements, studies of DNA synthesis and techniques with anitbodies against proliferation markers have been used. The determination of T_{pot} with such techniques allows apparently the decision which individual tumors, cf head and neck carcinomas, should receive conventional or accelerated radiotherapy.

Experimental data and clinical experience have demonstrated that hypoxia plays a decisive role in some tumors. However it is necessary to select these tumors. Several attempts have been made to measure blood flow, oxygen supply and vascularization of tumors. These studies have included rather complex techniques as PET and NMR-spectroscopy. These methodologies can also be used for metabolic studies (energy metabolism, glucose metabolism, pH etc.). Such data are of importance for combined treatments with hyperthermia.

Through these studies on individual human tumors much insight has been gained on the biology of tumors and its implications for radiotherapy. This leads to individualization and optimization of tumor therapy.

22

Surgical and adjuvant treatment of rectal cancer

J.-. Barras * , U. Metzger°

* University Clinic for Visceral and Transplantation Surgery, Inselspital, Bern, Switzerland
° Stadtspital Triemli, Zurich, Switzerland

At time of diagnosis, about 75 % of patients with rectal carcinoma present a disease stage allowing a potentially curative therapy.In fact only 60 % of patients treated in curative intent will be cured. The major part of this treatment is the operative excision of the disease either by anterior resection or by abdominoperineal excision, rarely by local excision. Much more than in surgery for colonic carcinoma, the result of this act depends on the quality of the surgeon. This quality can be indirectly measured by the rate of sphincter saving operations , which should reach about 80 % or more, and by the rate of locoregional recurrence in the pelvis. Recurrence in the suture line is a sign of very poor surgery. Local failure is not only influenced by the surgical skill but is highly stage - dependent. In multicentric series, 20- 50 % of the patients with advanced local disease treated by surgery alone present a local failure diagnosed mainly within the first two years after surgery. In more than 2/3 distant metastases will be found within further six months.In nodal-positive cases, principally those having a N2 or N3 stage, the pattern of recurrence is marked by a high rate of distant metastases.

This bipolar pattern of recurrence represents the challenge of treatment mainly in stage II (local advanced nodal-negative) and in stage III (nodal positive without distant metastasis) Adjuvant treatment has been directed mainly to these stages. An improvement of local control has been achieved by adjuvant preoperative radiotherapy , but without improvement of long term survival.The results of postoperative radiotherapy alone were disappointing. The effects of postoperative adjuvant chemotherapy alone were minimal. An improvement of overall survival, of disease free survival and a decrease of local failure have been achieved by combined adjuvant treatment (i.e. postoperative radiotherapy enhanced and supplemented by postoperative chemotherapy with 5-FU) conducting to a broad acceptance of this kind of adjuvant treatment as the gold standard of adjuvant therapy of rectal carcinoma. Despite these results, many authors are convinced that another timing of this combined adjuvant treatment, modification of the rythm of application of radiotherapy and modulation of the 5- FU application could further improve the results of adjuvant therapy and perhaps decrease long term complication rate.

23

CD44 SPLICE VARIANTS IN TUMOR METASTASIS.

Kaufmann, M., Heider, K.-H., Sinn, H.-P., Sleeman, J. P., Kondo, K., Ponta, H., Pals, S. T., Zöller, M., Herrlich, P.*
*Kernforschungszentrum Karlsruhe, Institut für Genetik, Postfach 3640,
D-7500 Karlsruhe 1, Germany

Despite the proposed role of a large number of molecules in the metastatic spread of tumor cells, a few "bottleneck" molecules appear to be decisive. One of these "bottleneck" properties involves the expression on the tumor cell surface of specific splice variants of the ubiquitous transmembrane glycoprotein CD44. The limiting function of these splice variants is documented by three types of observations: i) Several non-metastasizing rat tumor cell lines can be converted to full metastatic lines by transfecting expression clones of CD44 variants carrying the v6 exon. Transfectants form lymph node, lung and other distant metastases upon subcutaneous injection. ii) Antibodies to a v6 epitope retard or even prevent metastasis formation. The outgrowth of tumor cells in the draining lymph nodes is inhibited suggesting an early role of CD44 v6 variants in the metastatic spreading. iii) Antibodies to v6 detect surface expression of CD44 variants in many human cancers while normal tissues are by and large negative. In colon cancer, v6 epitope was detected with increasing frequency with advanced stages reading 100% in Duke III carcinoma and in metastases. In mammary carcinoma, an impressive correlation with poor survival has been observed in a retrospective study of 59 primary tumors. The surface expression of CD44 v6 epitope seems to be a better indicator of prognosis than erbB2 EGFR or even lymph node status. This observation strongly supports the notion that CD44 v6 variants confer limiting properties to cancer cells in the generation of metastatic clones out of the primary tumor location. - Studies with mutant proteins in animal systems have yielded evidence that the CD44 v6 variants act as specific adhesion molecules.