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VASCULAR DENSITY IN CANCER AS A PREDICTIVE ASSAY.

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The pattern of vasculature has since long been recognized as an important factor in determining the response of tumors to treatment with radiation or chemotherapeutic agents. Morphometric investigations will be reviewed performed with the purpose to estimate quantitatively the degree of vascularization in tumors, and relate it to the therapeutic efficacy. Most of the available experience has accumulated with lesions of the uterine cervix in different stages. The degree of vascularization in the different regions of this type of tumors was found to vary considerably. However, as indicated by variance analysis, the *intra*-tumoral inhomogeneity was smaller than that seen *inter*-tumorally. In the majority of cases a close relationship was noted between vascular density and survival after radiotherapy, large densities being associated with increased control rates. The predictive value of vascular density indicated by these observations suggests that the development of a graded vascularization index, complementary to the TNM system, would provide more accurate prognosis and the possibility for a more individualized treatment than practiced to-day.

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TISSUE OXYGENATION PREDICTS SURVIVAL IN ADVANCED CERVICAL CANCER

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The clinical importance of tumor hypoxia remains uncertain since valid methods for the routine measurement of intratumor O_2 tensions in patients have so far been lacking. A clinically applicable procedure has been established which enables the determination of intratumor O_2 tensions in advanced cervical cancers by use of a computerized polarographic needle electrode system. Tumor oxygenation as measured by this method represents a novel feature which can be individually determined for each tumor and which is independent of other known oncological parameters. The results of an open prospective clinical trial to evaluate the prognostic significance of tumor oxygenation based on the survival data of 32 patients are presented. Twenty patients received radiotherapy (RT) alone and 12 patients were treated with RT combined with chemotherapy. After a median follow-up of 25 months (range 5-42 months), Kaplan-Meier-life table analysis showed significantly lower survival and recurrence-free survival for patients with a median $pO_2 \leq 10$ mmHg compared to those with better oxygenated tumors (median $pO_2 > 10$ mmHg).

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TUMOUR CELL PROLIFERATION AS A PREDICTOR

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Rapid tumour cell proliferation is gradually being recognised as a major biological cause for the failure of conventional radiotherapy to eradicate some human tumours. Evidence for this has come from analysis of split-course radiotherapy schedules and those in which the overall time varied. However, some of the most compelling data has arisen from flow cytometric analysis of tumour cell proliferation measured by infusion of bromodeoxyuridine *in vivo*.

This relatively new technology has enabled extensive studies of proliferation in human tumours which was not previously possible with the existing methods. Dynamic cell kinetic parameters can be obtained safely, rapidly, quantitatively and from only one biopsy. These attributes satisfy many of the criteria required from a predictive assay.

Measurement of the potential doubling time (T_{pot}) has shown that many human tumours (50% or more) may possess the characteristics which might benefit from shortening the overall treatment time. The studies show tremendous heterogeneity in proliferation characteristics between both tumours of the same type and those of difference origin, emphasising the need for individual assessment.

The T_{pot} measurements are being made in many centres throughout the world and are being incorporated into randomised clinical trials such as the EORTC trial 22851 and the CHART trial, both of which are multi-centre. Data from these trials and other studies suggest that T_{pot} may have predictive value in suggesting which patients may benefit from accelerated radiation treatment and those who may be best treated by conventional or hyperfractionation. The technique is now at the stage when it could be routinely incorporated into clinical management for certain patient groups.

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GENE ALTERATIONS AND RESPONSE TO DRUGS

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Increased understanding of the genetic and molecular basis of drug resistance has recently yielded promising results. In most cases, the selection of drug resistance has been determined in cell culture and animal models, but evidence from molecular analysis of human tumors suggest that similar mechanisms may also operate in clinical drug resistance.

Decreased intra-cellular accumulation of drugs is one of the most common mechanisms of cancer drug resistance. This may be due to reduced drug influx (methotrexate) or to an increased of drug efflux. The most important clinical example is the activation of MDR1 gene encoding for the putative drug efflux pump associated with multiple drug resistance, P-Glycoprotein.

Drug resistance may also be due to ***altered drug metabolism*** as reported for purine or pyrimidine analogs with reduced levels of the kinases and phosphoribosyl transferases involved in the convertion of prodrugs in cytotoxic derivatives. Conversely drug-inactivation or alterations in co-factors may also confer resistance to these antimetabolites.

The drug resistance of tumor cells may also involve ***alterations of the intracellular drug target.*** Alteration of dihydrofolate reductase (gene amplification), thymidilate synthetase and DNA topoisomerases has been shown to be associated with resistance to specific drug-inhibitors of these enzymes.

An other aspect of tumor cell drug-resistance such as alkylating agents, is ***the repair of DNA damages.*** Increased repair capacity as reported for CDDP and alkylating agents may well confer resitance to multiple agents.

Additional studies are needed to identify as yet unrecognized resistance mechanisms and to develop specific resistance reverting agents.

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CELL KINETICS AND RESPONSE TO DRUGS.

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In clinical oncology, clinical and pathologic stages have been regarded as the only prognostic factors and have been used to plan therapy for several decades. Clinical experience has shown that the outcome is largely unpredictable on the basis of stage information and that patients with advanced disease, who are the most intensively treated, are the most resistant to systemic treatment. Cell kinetics has been evaluated as a marker of clinical aggressiveness and, based on evidence in experimental tumors, as a potential indicator of response to conventional chemical treatments. Proliferative activity, defined by using different approaches, has proved to be an established and independent prognostic marker for many human tumor types, whereas accumulating evidence shows that it is not an absolute indicator of response to therapy. A high proliferative activity is not indicative of response to chemotherapy in colon cancers or in malignant melanomas at all stages. In other tumors, such as breast cancer, the direct relation between proliferative activity and response to drugs eventually disappears with progression of the disease. These findings can be explained on the basis of intrinsic drug resistance. Retrospective analyses on large series of breast cancers and ovarian cancers have identified cell kinetic subgroups of patients which respond to treatment with conventional agents specific for drug type or intensity. In vitro clonogenic and proliferative assays performed on clinical tumors have shown that proliferative activity is an indicator of response to hyperthermic treatment in malignant melanoma or to new drugs such as taxol and taxotere in ovarian cancer.

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DETERMINATION OF CISPLATINUM DNA ADDUCTS BY SPECIFIC ANTIBODIES IN VITRO AND IN VIVO: GENETIC POLYMORPHISM IN DNA REPAIR AS A PREDICTIVE FACTOR FOR ACCURATE DRUG DOSIMETRY

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The chemotherapeutic effects of Cis-platinum (cis-Pt) are due to the adducts formed with DNA which inhibit both DNA replication and transcription. DNA repair enzymes excise the cis-PT -DNA adducts thus eliminate the cytotoxic effects of the drug. Using antibodies againts cis-Pt -DNA in an enzyme-immunoassay we have observed a genetic polymorphism among different individuals in their DNA repair capacity as expressed in the half-life time of cis-PT-adducts. Cell cultures from treated and untreated persons exhibit differences of more than 1000 fold in DNA repair levels. In vivo studies are performed in which the half-life time of cis-Pt-DNA adducts in treated patients is correlated with their clinical response. Using in vitro studies, we treat isolated lymphocytes prior to chemotherapy to determine their DNA repair capacity. Such an approach may have a high predictive value in chemotherapy.

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