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MODIFICATION OF HYPOXIA IN RADIOTHERAPY - OVERVIEW OF THE PROBLEM.

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The importance of tumor hypoxia for the outcome of radiotherapy has been under investigation for decades. Numerous clinical trials have been conducted, but most were inconclusive. The reason for this may either be that no true difference exists or that the trials have been too small to detect a difference. An answer to such questions can be obtained by meta-analysis in which the results from **all** clinical trials addressing the specific question of hypoxic modification in solid tumors undergoing primary radiotherapy be analyzed. A literature survey identified more than 10,000 patients treated in 75 **randomized clinical trials**, applying hyperbaric oxygen, hypoxic radiosensitisers, oxygen or carbogen breathing, and blood transfusion. The tumor sites were bladder, uterine cervix, CNS, head and neck, and lung. The meta-analysis has demonstrated significant improvement following hypoxic manipulation in especially tumors of the head and neck. This benefit was most pronounced regarding local control, but a significant effect with respect to survival was also found. The results indicate that the biological issue related to hypoxia may be a sound rationale, but hypoxic tumors *per se* need to be better identified.

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EUROPEAN ETHANIDAZOLE TRIAL IN HEAD AND NECK CANCER

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RTOG CLINICAL TRIALS WITH ETANIDAZOLE

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The RTOG conducted a Phase III trial of the hypoxic cell sensitizer, S-2508 (etanidazole) combined with conventional radiation therapy (RT) in patients with advanced head and neck cancer. The trial was open from June 1986 to October 1991 with 554 patients entered. The objectives were to determine the effect of SR-2508 on, local-regional control and tumor-free survival both measured at two years. The number of patients was increased during the trial because 27% of the patients received less than 14 drug doses either discontinued because of drug toxicity of patient refusal. RT was 66-74 Gy in 33-37 fractions. The drug was given at 2 gm/m_2 three times per week for 17 doses with a total dose of 34 gm/m_2. Pharmacokinetics was done on the majority of patients. The drug toxicities included 17% Grade I and 6% Grade II peripheral neuropathy (PN), no Grade III or Grade IV. The PN resolved in 6/14 Grade II patients. There was no central neuropathies. There was 10% allergic reaction to the drug, and 28% nausea and vomiting. The acute and chronic RT toxicities were similar between the RT only arm and the RT plus drug arm. The results are still coded. The final analysis of the study is anticipated in December 1993.

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Can tumour hypoxia be predicted?

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The oxygenation of malignant tumors is determined by the oxygen delivery and the oxygen uptake. The oxygen delivery mainly depends on the perfusion rate per unit weight, the hemoglobin content of the arterial blood, the hemoglobin saturation and the shape of the oxygen saturation curve. The weight-related perfusion rate is modulated by temporal and spatial inhomogeneities. The hematocrit value within tumor microvessels fluctuates around values below the mean arterial hematocrit. The shape of the oxygen saturation curve is directly influenced by the perfusion-related accumulation of metabolic waste products. Considering oxygen consumption rates, supply limits uptake in most experimental tumors. Since metabolic turnover is lower in human tumors, a proliferation dependent oxygen consumption has to be expected in most human tumors. Since the actual tumor perfusion and metabolic rates cannot be predicted at the present time, the tumor tissue oxygenation has to be estimated directly by invasive or indirectly by non-invasive techniques.

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NEW APPROACHES TO OVERCOME RADIOBIOLOGICAL HYPOXIA: EXPERIMENTAL EXPERIENCE

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The presence of hypoxic cells in animal tumours is recognised indirectly, from functional radiobiological tests, by hypoxic cell stains based on the bioreduction of nitroimidazoles and the more macroscopic assessments made with oxygen microelectrodes. There are two types of hypoxia, the classical diffusion-limited version and transient hypoxia of whole cords as individual vessels close down for a period of minutes or hours. Recently a revival of interest in carbogen has shown significant benefits in experimental tumours (SER = 1.4). Similar benefits are obtained with large doses of nicotinamide, which seems to reduce intermittent vessel closure. The two sensitizers give a value of 1.8 - 2.2 with multiple fraction x-ray schedules, mimicking clinical treatments. A further gain is obtained if the treatments are given in a shorter period e.g. 2-3 weeks instead of in the conventional 6-7 weeks. The concept of ARCON (accelerated radiotherapy with carbogen and nicotinamide) is now being cautiously translated into clinical practice, with phase I/II studies to determine the dose reduction needed to avoid excessive normal tissue reactions.

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NEW APPROACHES TO OVERCOME RADIOBIOLOGICAL HYPOXIA - CLINICAL EXPERIENCE

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Hypoxic cell radiosensitization is a major issue of clinical research. Despite a considerable experimental and clinical effort, there is no repeated - and no randomized - evidence that our attempts in overcoming hypoxia have advanced patient care. Nevertheless, this failure doesn't detract from the relevance of hypoxia in clinical radiotherapy.

After the large majority of randomized trials using radiosensitizers of the first or second generation such as metro- and misonidazole, have failed to show benefit, efforts have been directed toward the development of compounds where a greater degree of radiosensitization could be achievable: the main axes of research encompass the testing of drugs of similar potency on hypoxic cells but of lower toxicity, the administration of compounds of higher potency and the application of local measures to increase intratumoral concentration of the radiosensitizing agent. We must await the results of clinical trials based on these mechanisms. Other avenues of research, such as testing artificial blood substitutes, agents enhancing the oxygen off-loading, the effect of bioreductive drugs in artificially hypoxic tissues and vaso-active agents on blood flow are under clinical investigations.

In the past, hypoxia has too often been looked at as a biological factor in isolation, instead of considering this parameter of radioresistance as part of a multifactorial process. The modulation of hypoxic cell radiosensitization processes by variations in radiotherapy fractionation could be a first step to a better integration of our radiobiological knowledges into the clinical field.