Third International Meeting on Progress in Radio-Oncology

March 27—30, 1985

VIENNA, AUSTRIA

ABSTRACTS

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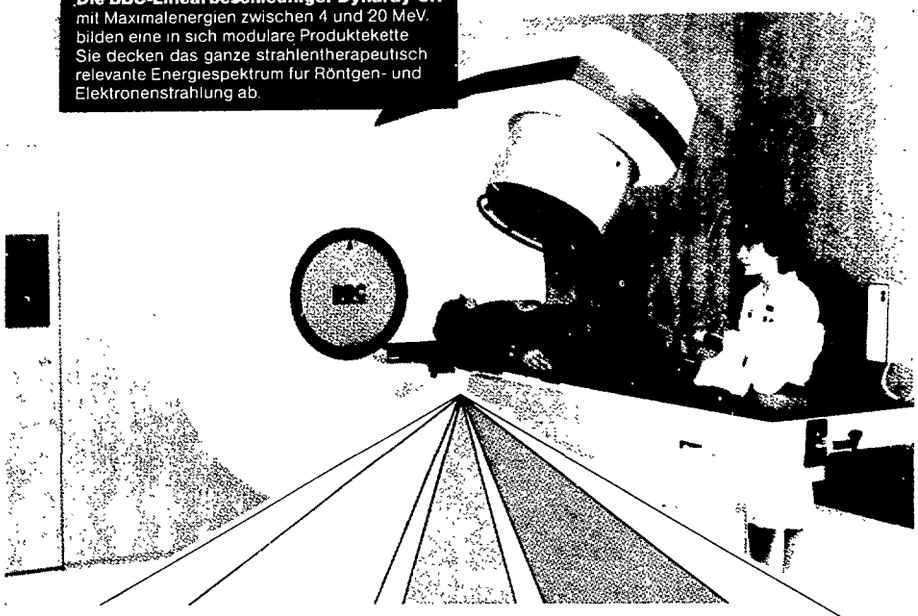

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(NOT FOR PUBLICATION)

Particular thanks are due to
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INTRODUCTORY PAPERS

Thursday, March 28, 1985

IAEA ACTIVITIES IN THE FIELD OF RADIOTHERAPY

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The IAEA has rich experience in the peaceful applications of nuclear energy and has therefore dealt with problems of radiotherapy on a rather large scale, from the setting up of radiotherapy services in countries with hitherto had none, to supporting research investigators on actual trends of radiotherapy both in industrialized and developing countries.

At present, the IAEA has three co-ordinated research programmes (CRP) on improvement of results of radiotherapy of cancer. One of them deals with applying high LET radiation (neutron-capture therapy and neutron, proton, pimeson beams, etc.) for non-conventional radiotherapy in cancer. Another two deal with combining conventional radiation with chemical (hypoxic cell modifiers, potential lethal damage repair inhibitors, some anti-cancer drugs) and physical (hyperthermia) means. These CRP's have participants from 23 countries, of which 12 are developing countries. As a rule, the IAEA donates contracts to participants from developing countries and signs research agreements with participants from industrialized countries. The IAEA provides financial support to enable all CRP participants to take part in research co-ordination meetings (RCM) which are organized by the Agency.

In connection with the above-mentioned CRP's, three RCM's have so far been held. They showed that the IAEA plays a significant role in co-ordinating the efforts of participants, in the exchange of information, and in increasing the standard of investigations. Unfortunately, at present, no radiation modifier is available for routine treatment since all are in the various phases of implementation into clinical practice, from experimental investigations to clinical trials. The same can be said about high LET radiation. However, hyperthermia is regarded as one of the prospective methods that will be applied in the near future in most cases of local cancer, but because of the high cost of the hyperthermic machines they are not available in many countries.

The technical assistance programmes on setting up of brachyradiotherapy services in countries which hitherto had none are going ahead successfully. The problem of trained staff ist being solved by offering fellowships and carrying out training courses. Training courses on brachyradiotherapy of carcinoma of the cervix started successfully in Egypt in 1983 and will be repeated there annually until 1987. Similar courses, and also training courses on general problems of radiotherapy, are planned to be held regularly once a year in the South-Asian region.

It is evident that successful resolution of technical and scientific problems of radiotherapy demands further support of clinical and basic research on main trends in radiotherapy, and close co-operation of scientists. The IAEA activities serve this goal and may be regarded as an important step towards resolution of the problem of progress in radio-oncology.

PREDICTION OF RESPONSE OF TUMORS TO RADIATION TREATMENT

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To increase the likelihood that a new treatment method which is being evaluated by the technique of a phase III clinical trial will be shown to be more effective when it is may require that patients be stratified on a more sophisticated basis. It is not likely that the new treatment will be of greater efficacy for all patients who are accessed into a trial according to current methods of patient stratification. The present phase III trials usually stratify only as to histopathologic type and grade, tumor size, anatomic site, patient's age and sex. There are now several anatomic, physiological or biochemical parameters which could be monitored on a prospective basis. This is a potentially rewarding and largely unexplored area of research. The goal would be to determine values for one or more of these parameters before and during fractionated radiation treatment and examine for correlation between those values and tumor response. For the measurements to be of predictive value, the tumors must be heterogeneous with respect to those parameters. The correlation will have to be strong. If the monitoring of the tumor is to be of clinical value. There must be a very low rate of false "positive" readings. This is true if a "positive" value is to be the basis for changing the treatment strategy of the individual patient.

One of the parameters of potential predictive value is measurement of cell proliferative activity. This can be monitored by flow cytometric technique with resulting information of the age density distribution and the extent of ploidy. There has been limited experience using a PETT with ^{11}C, thymidine to assess, non-invasively the proliferative activity. This approach is non-invasive and could be employed for deep-seated lesions. Another area of considerable interest is, of course, evidence for the presence of hypoxic sells. These could include:
hematocrit; arterial or venous pO_2; intercapillary distances measured on biopsy specimen; tumor blood flow; uptake by the tumor of substances which indicate the presence of hypoxic cells (2-deoxyglucose, misonidazole, etc.), ^{31}P NMR spectra, polarographic estimates of tissue pO_2, etc. Another parameter would, of course, be evidence for immune rejection reaction against the tumor and the immune status of the patient.

As many patients are receiving concurrent or sequential chemotherapy, there should be predictive value in the concentration of drug in individual tumor. Such measurements are limited to accessible tumors. Techniques are available which measure drug concentration in small biopsy samples, e.g., ($\leq$20mg). Adriamycin is one such drug.

The presentation will review some of these approaches to predicting tumor response to radiation.

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ALTERED FRACTIONATION

Thursday, March 28, 1985

DEPENDENCE OF NEOPLASTIC TRANSFORMATION ON DOSE RATE AND MULTIFRACTIONATION: COMPARATIVE RESULTS FOR γ-RAYS AND NEUTRONS

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An important limitation to the effectiveness of radiation therapy directed against primary cancers is the onset of late-developing normal tissue damage. A focus on late-developing degenerative changes reflects in facts that patients are living longer after therapy, and that extended lifespans have become possible without unacceptable levels of early-expressed damage in normal tissues.

Among the late effects of concern is the induction of new primary cancers. For example, the effective treatment of Hodgkin's Disease is now well known to be accompanied by significant risks of inducing second malignancies which are, for all tumor types, about 7.6% for radiation alone and 12.1% for radiation plus adjuvant chemotherapy (N. Coleman et al. (1982): Cancer Surveys 1:733-744).

In an effort to understand the fundamental processes which underlie radiation-induced tumorigenesis, some years ago we started to study of the radiobiology of neoplastic transformation in vitro. We have used a line of rodent cells, developed in the laboratory of the late Charles Heidelberger, designated 10T^1/2. Transformed cells of this type produce fibrosarcomas in appropriately treated C3H mice. Our results show a qualitative agreement with observations made in vivo and, therefore, they offer some general guidance for clinical practice.

Single-dose and protracted-dose data will be presented for X- and γ -rays, and for fast neutrons, particularly for fission-spectrum neutrons. In summarizing terms, the data to be reviewed suggest that dose protraction with a low-LET radiation should reduce the risk of second tumors outside of the field whereas the reverse could be the case for fast neutrons of low average energy. The situation within the field is more complex when comparing single vs. protracted doses, of low- vs. high-LET radiations.

These studies have been supported by the U.S. Department of Energy, Contract No. W-31-109-ENG-38, and the U.S. National Cancer Institute, Grant No. CA 29940.

(a) Deceased, 7 May 1984.

SMALL DOSES PER FRACTION IN RADIOTHERAPY : LIMITING TOTAL DOSES

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If the effect of n multiple fractions d is represented by $E = n(\alpha d + \beta d^2)$, the ratio α/β can be obtained from a knowledge of iso-effect doses for different fractionation schedules. However, absolute values of α or β can only be obtained if relevant clonogenic assays are available. Nevertheless, organ radiosensitivity is indicated by the absolute value of the isoeffect doses for organ dysfunction. In particular, α/E or the Extrapolated Total Dose enables the radiosensitivity of various organs and tissues to very low doses per fraction or to low dose rates to be compared. Radiosensitivity to multifraction irradiation may be more relevant to radiotherapy than the sensitivity to single radiation doses. Examples will be given and their significance discussed. Compared with the single-dose radioresistance, organs which respond at late times after irradiation move to a relatively more resistant listing in the sequence of radioresistance for multiple small fractions than organs which react early.

CLINICAL RADIOBIOLOGICAL STUDIES OF THE INFLUENCE OF DOSE PER FRACTION ON EARLY AND LATE RADIATION DAMAGE IN DIFFERENT NORMAL TISSUES

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Objective: The aim is to analyse the influence of dose per fraction on early and late radiation complications in patients treated with postmastctomy radiotherapy.

Approach: All breast cancer patients, who received postmastectomy radiotherapy in the period 1978-81 at Radiumstationen in Aarhus were treated with identical radiation field arrangement. However, the patients were treated at two different dose levels and with 2 different fractionation schedules +/- adjuvant chemotherapy.

Progress: 387 patients have been examined with respect to acute and late radiation damage in the skin, lungs and ribs. Further functional end points such as arm oedema, impairment of shoulder movement and lung symptoms have been registered as will as loco-regional and distant tumor control.

A preliminary analysis of the data has shown that patients treated with large doses per fraction had significantly increased late radiation complications in both skin (fibrosis and telangiectasis), lung (late fibrosis), and ribs (spontaneous fractures) compared to patients treated with small (app. 2 Gy)doses per fraction. It has also been found that these late radiation complications have clinical implications for the patients by causing increased risk of arm oedema, impaired shoulder movement and lung symptoms.

The dose modifications for the two fractionation schedules have been based on the NSD-formula, and this was found to be valid with regard to the acute skin reactions, whereas this was not the case for the late reactions. Better isoeffect models are available, e.g. the linear quadratic model. From this model it is possible to predict isoeffect for both acute and late radiation reaction in the same time and also for different tissues. Thus, the alpha/beta ratio calculated from the data in this material was approximately 10.0 Gy for acute skin reactions, but only 1.1 and 2.2 for late skin reactions (telangiectasis and fibrosis). For acute and late lung reaction the alpha/beta ratios were 4.2-6.9 Gy and 3.0-3.6 Gy, respectively, and finally the alpha/beta ratio for osteoradionecrosis was calculated to be 2.5 Gy. These clinical data are in agreement with experimental data.

The work was performed in collaboration with Jens Juul Christensen and Soren Bentzen, Department of Radiophysics, Radiumstationen, Aarhus, and E. Hjøllund Madsen, Department of Diagnostic Radiology, Aarhus Municipal Hospital.

THE COMBINATION OF BRACHYTHERAPIE WITH TELETHERAPIE

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Brachytherapy allows according to the volume- and time-effect relatively high dosage in a limited volume. Especially with long living permanent implanted radionuclides (e.g. I-125) exceptional high doses are applicable. The steep dose gradient at the periphery of the implant of course makes a supplementary percutaneous treatment necessary, especially if the tumor's border is not identified or there have to be irradiated lymph nodes in the neighbourhood.

Planning of combined radiotherapy needs biological weighing of the different applicated dose distributions and exact spatial superposition and addition of the isoeffect contours.

This paper offers a system, which satisfies this conditions. Clinical examples with different tumor localization will be demonstrated.

RADIATION THERAPY FOR POSTERIOR UVEAL MELANOMA

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In the United States in 1984, the American Cancer Society anticipates that there will be 2.000 new cases of primary malignant tumors of the eye. The most common primary malignant intraocular tumor is malignant melanoma of the choroid, comprising about 75% of all primary malignant tumors of the eye. Ophthalmologists have been familiar with these tumors for many years but there still remains considerable controversy regarding the best approach to diagnosis and treatment. The program presently under way as a cooperative venture between the Ocular Oncology Unit at the Wills Eye Hospital and the Hahnemann University Department of Radiation Oncology, employing various radioactive plaque treatment programs, is based on accurate dosimetry and has better control of complications than have been demonstrated in the Stallard studies of the past. The survival fort treatment using the radioactive plaque program is equivalent to if not better than the survival following enucleation.

A study of the use of helium ion radiotherapy for the treatment of posterior uveal melanomas is under way at the University of California, San Francisco, and the Lawrence Berkeley Laboratory. These two programs and the MGH/Harvard cyclotron study offer an opportunity to compare the results of treating patients with these three different treatment techniques. At present, all three methods of treatment in the hands of experienced ophthalmologists and radiation oncologists are yielding results that are equivalent to if not better than those achieved by enucleation with a major advantage being preservation of vision.

ABOUT DOSE - TIME - RELATIONSHIPS AT PROTRACTED LOW-DOSE-RATE BRACHYTHERAPY AND FRACTIONATED HIGH-DOSE-RATE SHORT-TIME-AFTERLOADING IN THERAPY OF GYNECOLOGICAL TUMORS

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In high-dose-rate short-time-afterloading at radiation therapy of gynecological tumors an adequate fractionation with reduced total dose is necessary considering the basically changed dose-time-relationships opposite to the conventional low-dose-rate brachytherapy. In addition to the careful clinical control of empiric found fractionation regimes for the primary and postoperative intracavitary and intravaginal afterloading-therapy at the cervix uteri and endometrium carcinoma, at which the tumor regression and relapses and also side effects of the bladder, the rectum and the vagina were investigated, a calculation of equivalent doses seems to be recommendable by means of mathematically formulated model conceptions after the NSD-conception. Changed exponents p for the number of fractions N depending on the overall treatment time were used for the retcalculations at slowly fractionated small volume brachytherapy opposite to a higher fractionated percutaneous large volume irradiation the NSD-conception was developed for. Knowing the compability and tumor effectivity of fractionation regimes discovered at mor than 2.2oo patients in over lo years the ret-values for different fractionation regimes with changed time intervals were calculated and compared concerning their radiobiological equivalence and practical use.

WEEKLY FRACTIONATED EXTERNAL RADIOTHERAPY IN UTERINE CARCINOMA - A FOLLOW UP STUDY

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Introduction:

With the introduction of "NSD" formula, a scientific and mathematic basis was attributed to time, dose and fractionation relationship in clinical radiotherapy. Amongst various advantages proclaimed, one was to evolve various treatment schedules and to compare their results.

The present communication is a follow up study of such patients treated by weekly fractionation schedules.

Clinical material:

Sixty two patients of gynecologic cancer were treated during 1975-76 at C.M.C. & Brown Memorial Hospital. All of them were diagnosed and staged clinically. Various routine investigations were done. They were treated by external radiotherapy with Co-60 by Eldorado "A" unit. 5 weekly doses of 580 rads were given to a field size of 15 x 15 cm^2 equivalent to 4.000 rads in 20 fractions over 4 weeks. It was followed by I/c radium or caesium application by Earnst applicator to give a dose of 4.000 rads at point A. The later was followed by one more weekly dose by shielding the centre to give an equivalent total dose of 5.000 rads at point B. The above scheme was used routinely except in 4 patients of carcinoma body uterus and 1 case of cervical stump carcinoma. The records of all above patients were reviewed and "TDF" factors were calculated for each one individually.

Observation:

Fifty one patients were free of disease and 11 had local disease, from a period ranging from 4 months of 84 months. One patient had recurrence in the nodes. The "TDF" factors ranged from 53 to 162.6. The complications encountered have been enumerated in table.

	Subcutaneous fibrosis	Bowel complications	Bladder complications	Bone changes
Mild	4	8	5	4
Moderate	6	20	3	3
Severe	1	15	2	1
Total	11	43	10	8

Patients who had complications had TDF above 134.

Discussion:

Tumor doses in this series were equivalent to conventional fractionated doses prescribed routinely but the complication rate is significantly high. This reflects the importance of quantity of radiation in time dose and fractionation relationship. The supralethal effect on normal tissue is amply illustrated in spite of a gap of 168 hours or more given for recovery of damage. We believe the use of such schedules for palliative radiotherapy. Normal tissues with rapid cell turn over should be avoided.

CLINICAL-RADIOBIOLOGICAL EXPERIENCES BY ULTRAFRACTIONED IRRADIATION

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It is 4 years ago that we began our new project on twice a day telecobalt irradiation, which means several irradiations within a day and concerns meinly the extended, poorly oxygenated tumors which cannot be treated by any other radiotherapy.

The usual rythm is 2 x 1,2 Gy per day, five times in a week, reaching thus 65-75 Gy as total dose.
The interval between the fractions are 6 or 7 hours in a day and 1o to 12 hours day after day. Most patients, 5o persons, had head and neck tumour, and the rest was suffering from either inoperable breast cancer or greatly extended malignant melanoma.

7o patierts have been treated, so far, most of them having a tumour of $T_{3-4}N_{1-3}M_0$ phase. In the case of head and neck carcinoma a new clinical experiment has been started since the beginning of 1984: the radiosensitiser MTDQ has been combinated with twice a day irradiation. Besides the clinical experience we also performed animal experiments on the histology of the irradiation in different rythm of Harding-Passay mouse melanoma.

Based on clinical and radiobiological data we think that the so called physical radiosensitivation or rather physical and chemical combination of radiosensitivation is suitable for the irradiation of hypoxic and anoxic tumours being not properly supplied with blood.

MULTIPLE FRACTIONS VERSUS SINGLE FRACTION A DAY IN ADVANCED LARYNGEAL CARCINOMA: A MATCHED PAIR PROSPECTIVE STUDY

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This study consists of 28 matched pairs selected from more than 1oo patients with advanced laryngeal carcinoma ($T_3T_4N_0N_+$), who were irradiated in AZVU since 1974 through 1983. These patients (1oo) are a part of a prospective study undertaken in AZVU since 1974 to improve the loco-regional contral probabilities for advanced H & N tomors without evidence of distant metastases. They were all meticulously staged, and underwent quality controlled high dose protracted shrinking fields radiation therapy with individual shell-masks, simulator, computer-dosimetry, repeated port-films and clinical vigilance from radiation oncologists in close co-operation with the otolaryngologists. One of the matched pairs had conventional fractionation (F) mostly with 2 Gy/F daily with a cumulative dose of 74 to 78 Gy in about 8 weeks. For the other pair, the treatment policy was to deliver 2 fractions of 1.25 Gy daily (MFD) with an average interval of 2 hours (range 1.5 to 4 hours). The total dose in this MFD group was 67.5 to 72.5 Gy delivered in about 6 weeks.

With a minimum follow-up of more than a year for the MFD group, it appears that the acute reactions and late effects are for both the groups acceptable and in the AZVU this MFD dose-scheme is more or less routinely followed whenever possible.

Whereas long term results must still be awaited, the local control probability with MFD appears to be better with resultant influence on survival.

RADIOTHERAPISTS' NEW LOOK AT BRONCHOGENIC CARCINOMA

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The preoperative results, literary evidence and our experience show, that radiotherapy can control localised carcinoma of the bronchus. However, the curative treatment is dominated by surgery and most patients referred to us are incurable. The clinical attitudes to radiotherapy are sceptical.

This paper will describe the histories of several long surviving patients who were treated by (1) conventional fractionation (2) six fractions in air (3) six fractions in hyperbaric oxygen. Also during the last decade, 54 patients were treated in Portsmouth by accel rated fractionation. Special attention will be paid to the control and survival of 8 patients with less advanced disease.

The acute and subacute tolerance of accelerated treatments were very good and the late changes rarely caused problems. The mild acute side-effects do not need a split-course. Pneumonitis becomes symptomatic only after exposure of relatively large volumes. Fibrosis in the treated area is inevitable but salvage surgery for recurrence is sometimes still possible. Squamous carcinoma can recur late and progress slowly over several years. In long survivals, there is an increased risk of a second primary carcinoma elsewhere in the bronchial tree.

Several reports suggest, that the control of the disease is improving with the frequency of conventional fractions (Brumm, 1983). Based on such observations and on our experience, a radical course of accelerated radiotherapy will be proposed for carefully selected early localised NSCC. The investigations will use all the modern imaging techniques to exclude metastases and to define the treated volume accurately.

HYPERFRACTIONATED RADIOTHERAPY OF CARCINOMA OF THE URINARY BLADDER

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The local control of bladder carcinoma is low after different treatment methods. In radiotherapy it necessiates the search for alternative methods in the treatment. With the following theoretical considerations a fractionation scheme with multiple daily fractions of low doses can be motivated. The dose-response curves, when tumour effect is compared with the late effect of normal tissue and linear quadratic formula is used, indicate a therapeutic gain in the low dose region (Fowler 1983). The same conclusion is obtained when the survival curves in presence or absence of oxygen are analysed. The oxygen enhancement ratio is decreased in the low dose level, which indicates a therapeutic gain to use low doses in the fractionation scheme (Littbrand and Révész 1969). The redistribution of cells after radiotherapy into different cell cycle phases indicates that repeated irradiations increase the possibility to hit cells in a sensitive phase. A fractionation scheme with multiple doses should be more effective than a conventional one when fast growing tumours are treated (Withers 1975).

168 patients with carcinoma of the bladder have been radomized to either of two fractionation schemes: 3 x 1 Gy a day, 5 times a week to a total of 84 Gy or 1 x 2 Gy a day, 5 times a week to a total of 64 Gy. In both schemes a split course technique was used. There was no significant difference between the two groups in the distribution of clinical categories. The follow-up time was at least 5 years. Cystoscopy and cytology 6 months after the start of radiotherapy showed a significantly better local clearance of the bladder in the hyperfractionated group. The same result was obtained in the analyses of survival.

The late complications came 1-3 years after the treatment. At that time more patients were alive in the hyperfractionated group than in the control group and therefore more patients were at risk. The difference in survival was 50%. Because of that one could expect more complications in the hyperfractionated group, which also was the case. 12 patients in the hyperfractionated group, compared with 4 in the control group, had late complications. A statistical analysis including the difference of patients at risk showed no significant difference between the two groups.

These results indicate a therapeutic gain of hyperfractionated radiotherapy compared with conventional radiotherapy in the treatment of carcinoma of the urinary bladder.

RADIOSENSITIZERS

AND

RADIOPROTECTORS

Friday, March 29, 1985

PROGRESS IN THE DEVELOPMENT AND APPLICATION OF NEW RADIOSENSITIZING AND CHEMOSENSITIZING DRUGS

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Hypoxic cell sensitization of experimental tumors irratiated with single doses is an established general phenomenon. However, clinical studies eg. with misonidazole have been disappointing although some benefit has been observed in some situations. Neurological toxicity has been the major limitation to dose escalation. Reoxygenation and the variability of in the extent of the hypoxia problem in human tumours may also be factors influencing sensitization in fractionated radiotherapy. New drugs are available some of which are in clinical trial eg. SR 2508 and Ro 03-8799. Experimental and clinical evidence suggest that the therapeutic ratios for these drugs should be superior to that of misonidazole.

There are several new approaches currently under laboratory and clinical investigation. These include studies on the influence of tissue anaemia on tumor response, the manipulation of oxygenation of tissue and its exploitation for increased therapeutic differential. New multi-functional drugs are now becoming available which combine two or more mechanisms for sensitization within the same molecule. Examples include nitroimidazoles carrying monofunctional, alkylating groups. These should allow new strategies to be developed for optimising both radiation and chemosensitization drugs. The experimental and clinical evidence upon which such strategies are based will be discussed.

ROLE OF RADIOPROTECTORS IN TUMOR THERAPY: FACTORS INFLUENCING THE EXTENT OF RADIOPROTECTION

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There is considerable experimental evidence showing that radioprotectors can protect various normal tissues from both acute and late radiation damage. The extent of normal tissue protection is, in general, higher than that of tumors, indicating that radioprotectors, notable WR-2721, can provide a therapeutic gain - however, whether this can be achieved depends on many factors and treatment settings. These have been studied in our laboratory in detail using C3Hf/Kam mice, and their brief summary is as follows.

Tumor Size: Tumor size plays a very important role in radioprotection. For example, an 8 mm leg fibrosarcoma (FSA) is not protected, while a nonpalpable leg tumor ist protected by a factor of 1.1 and lung micrometastases by a factor of 1.2. Tumor size affected protection against CY damage in a similar way. Although the same principle is applicable to other murine tumor as well, MCa-4 mammary carcinoma, for example, is protected more than FSA.

Tumor Hypoxia: Tumor hypoxia limits radioprotective activity of WR-2721 in both normal tissues and tumors. However, even under severe hypoxic conditions WR-2721 affords some protection. For example, tumor cells irradiation in situ under complete hypoxia were still protected by a factor of about 1.05.

Fractionated Irradiations: Two types of studies were performed. In the first, cure of 8 mm FSA exposed to 5 daily fractions was minimally affected by WR-2721. The protection factor was only 1.05. These mice, however, were protected against radiation-induced hair loss and leg contractures by PFs of 1.29 and 1.28, respectively, showing a significant therapeutic again. In the other type of study, lung micrometastases were exposed to clinical dose ranges of radiation in 5 equal doses (from 180 to 340 rads) with 6-hour intervals between doses. WR-2721 was similarly protective here as in the case when large single radiation doses were used. This could have a significant beneficial implication for the clinical use of WR-2721.

Tumor Bed Effect: Because of vascular damage, irradiation of tumor slows tumor growth but results in reduced radiocurability. Our experimental data show that radioprotection against the tumor bed effect can protect tumors in the tumor growth delay assay, but it can act beneficially by preventing tumor bed effect-induced reduction in the tumor radiocurability.

Timing of WR-2721 Administration: We found that gut and testes were maximally radioprotected when WR-2721 was given approximately 10 minutes before irradiation, whereas FSA micrometastases were maximally radioprotected when WR-2721 was given 30 to 90 minutes before irradiation. Therefore, in order to maximize the therapeutic gain the tumor should be irradiated at the time of the largest difference in radioprotective effect between the critical normal tissues and the tumor.

Carcinogenesis: WR-2721 greatly protected against radiation-induced carcinogenesis. Radiation to the leg with 3400 to 5700 rads caused 93% of the mice to develop sarcomas in the irradiated tissue. WR-2721 given before irradiation reduced this tumor incidence to only 30%.

Protection Against Immunosuppression: WR-2721 protected against radiation-induced immunosuppression by PFs of 1.4 to 2.5, depending on the type of immune reaction. This protection can benefit tumor radiocurability as well as reduce immunosuppression-mediated susceptibility to infections.

Diethyldithiocarbamate (DDC): DDC is also a good radioprotector, especially for hematopoietic tissue (PF 1.59). Because of its low toxicity, it might be a useful radioprotector in certain settings as well.

Thus, our data show that radioprotectors can successfully be used for increasing therapeutic gain in radiotherapy (and chemotherapy); the summary of PFs is shown in Table 1. The extent of radioprotection achieved was influenced by many factors discussed above. A better understanding of these factors will lead to proper and beneficial use of radioprotectors when combined with radio- and chemotherapy.

TABLE 1

Protection Factors in WR-2721 Produced Protection Against Radiation Damage of Normal Tissues and Tumors of C3Hf/Kam MiceA.

A. Normal Tissues (Single Radiation Doses)

	Acute Damage	Late Damage
Bone Marrow	>2	
Esophagus	1.58	
Jejunum	1.64	
Colon	1.72	1.58
Hair Follicles	1.24	
Testis	1.54	
Immune System	1.4-2.5	
Leg Mobility		1.51
Tumor Bed		1.52

B. Tumors

	Single Dose	Fractionated Irradiation
FSA 8 mm	0.94	1.05
FSA Nonpalpable	1.1	
FSA Micrometastases	1.21	1.19
MCa-4 8 mm	1.23	

VASCULARITY AS A PREDICTOR OF RADIATION RESPONSE: ITS POSSIBLE PRACTICAL USEFULNESS IN SELECTING CASES FOR TREATMENT WITH RADIOSENSITIZERS

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The results of an investigation will be reported in which a total of 79 patients with larynx tumors, St. III, treated with radiotherapy at the Alma Ata Institute, were analysed in regard to tumor vascularity and its possible relationship to survival. The vascularity was determined by morphometric analysis of fixed and stained histological sections prepared from biopsies, and classified according to the capillary density arbitrarily as "poor", "medium" and "rich". The corresponding 5-year-survival was 31, 41 and 77 per cent, respectively. For the entire material 5-year-survival of 33 per cent was calculated.

The results indicate that a considerable variation of vascularization occurs in tumors of the same type and stage, and a relationship exists between capillary density and survival in a general agreement with earlier observations made with cervix carcinoma cases. The relationship can be attributed to a larger hypoxic cell fraction in the group of poorly, than in the group of well vascularized tumors. It is likely that any major improvement of the survival by treatment with hypoxic cell sensitizers occurs only in the former group. Analyses will be presented to demonstrate that improvement of treatment solely in one sub-group of tumors may not show up as a significant change of the survival in the entire material. This may provide a further explanation for the failure of the clinical trials so far to demonstrate any effectiveness of radiosensitizers in improving therapeutic results. Clinical trials with sensitizers may require the selection of appropriate test tumors. Such a selection may be facilitated by a simple, histologic determination of tumor vascularity before therapy is initiated.

THE COMPETITION MODEL OF RADIOSENSITIZATION AND RADIOPROTECTION

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The well known equation oer = $(m(O_2) + K) / ((O_2) + K)$ can be derived starting with two different sets of assumptions: (1) that there are two types of damage induced by radiation one of which can be repaired (Howard-Flanders); and (2) that a single type of damaged target radical can react with naturally-occurring sensitizer F, or a protector S (Alper). Assumptions (1) are not adequate to explain the protective effect of sulphydryl groups under hypoxic conditions. Assumptions (2) cannot explain the result, if reduction in intrinsic SH decreases the K value, but does not affect m. It therefore seemed of interest to derive a formula combining assumptions (1) and (2). A parameter x is introduced which is the ratio of reparable to irreparable lesions, as in the Howard-Flanders derivation.

It can be shown that:

$$\text{oer} = \frac{\left(\dfrac{F+S}{F+\dfrac{S}{(x+1)}}\right) O + (F+S)}{O + (F+S)}$$

where $F = K_F(F)$, $S = K_S(S)$, and $O = K_O(O_2)$.
This equation has the general form $\text{oer} = (m(O_2) + K) / ((O_2) + K)$.

The relative sensitivity (DMF) of cells with different levels of protector S_1 and S_2 under hypoxic conditions can be shown to be: -

$$\text{DMF} = \frac{x\left(\dfrac{F}{F+S_1}\right)+1}{x\left(\dfrac{F}{F+S_2}\right)+1}$$

It can be shown that if we have values for 3 parameters: (1)m; (2) the ratio S_1/S_2, and (3) the DMF when S_1 is changed to S_2, then the model predicts the ratio F/S and the value of x.

The interpretation of experimental data obtained with cells with depleted GSH due to BSO or DEM treatment, or to genetic deficiency, will be discussed in terms of this model. The interaction between GSH depletion and sensitizers will be examined.

The mathematical model is very similar to that previously described by C. Koch.

EXPERIMENTAL WORKING OUT AND CLINICAL TRIALS IN USSR THE METHOD OF HYPOXYRADIOTHERAPY OF MALIGNANT TUMORS

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Abstract not arrived by deadline.

CLINICAL PHASE-I/II-STUDY IN HYPOXYRADIOTHERAPY

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In co-operation between the GDR and the USSR experimental data for clinical use of hypoxyradiotherapy has been obtained since 1974. These investigations were carried out in laboratory animals and in big mammals (beagle-dog, pig) as well as in spontaneous mamma-tumors at bitches and have been published manifoldly.

They proved in different species of animal and different systems of organ as well as in the field of metabolism, that by using hypoxia at the time of irradiation an obvious protection of normal tissue can be obtained. The executed pathomorphological (including electron microscopy), biochemical, hematological, electrophysiological and veterinar-clinical investigations as well as observations of late effects of that animals showed that the acute hypoxia (10% O_2) is well tolerated and shows no late effects.

On the basis of these results now we have started the clinical test of hypoxyradiotherapy at the Radiologische Klinik und Poliklinik der Akademie für Ärztliche Fortbildung der DDR am Bezirkskrankenhaus Karl-Marx-Stedt with the aim of increasing the tumor dose at simultaneous preservation of the irradiated normal tissue (protective factor in animal tests 1.2 - 1.3). The authorization for the clinical test in the form of a phase I/II-study was given at May 9th, 1983 by the minister for Public Health of GDR.

There was developed a technical system producing a respiratory gas mixture with 10% oxygen part out of air and nitrogen. The composition of this gas mixture is controlled by a gas analyzer. The gas mixture is filled in Douglas-sacks, out of which the patient respired. Hypoxyradiotherapy is carried out after consent in writing of the patient who is adequate enlightened on this method. There is a interdiscipline treatment team: radiologist, anesthesiologist, neurologist, biologist, biochemist and physicist.

After consent in writing of the patient and exclusion of contraindications (heart-circulatory system, lung function, blood diseases, metabolic diseases, kidney troubles, neurologic diseases and other) clinical and paraclinical investigations are carried out to estimate the tolerance of hypoxia (chest radiography, electrocardiogram, vital capacity, hematological status, metabolic status, lactate, enzymogram).

If these investigations yield no contraindications, a test hypoxia is made with the patient (10%, 15 min.) with simultaneous control of electrocardiogram, blood pressure, pulse-frequency, respiratory-frequency, pO_2-course figure (capillary and transcutaneous measure), acid-base-status and lactate. If this test agrees unobjectionable with the patient, hypoxyradiotherapy is possible. During the irradiation treatments under hypoxia electrocardiogram, respiratory-frequency and pO_2 (transcutaneous) is controlled.

For criticizing the tolerance of hypoxia the following investigations are carried out after finishing the treatment: clinical whole body investigation (2/week), neurological status (1/week), cardiological special investigation (2/week), biochemical liver and kidney status (2/week), metabolic status (2/week), hematological status (2/week) and enzymogram (2/week). There is also made inquiries about the neurological status. All findings are led to the electronic data-processing. The criticizing of the tumor reaction is made according to the criteria of EORTC. With the above-mentioned radio-oncological aim hypoxyradiotherapy was carried out op to now in patients with tumors of ear, nose, and throat areas, bronchial tumors, esophagus tumors, brain tumors and other. In addition we have had two-term half-body irradiations under hypoxia in patients with multiple metastases. The results of the clinical phase I/II-study are presented. An estimation of tolerance of hypoxyradiotherapy is given and also a judgement of tumor reaction. The investigations were carried out within the scope of the RGW-complex program "malign tumors" in co-operation with the Oncological Scientific All Union Centre of the Academy of Medical Sciences of the USSR, Moscow. After finishing this phase I/II-study a randomized international investigation between the GDR and the USSR is planned.

CORRELATION OF THE STRUCTURE AND EFFECTS OF A DIHYDROQUINOLINE TYPE HYPOXIC SENSITIZER AND A RADIOPROTECTIVE AGENT

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Correlations of the chemical structure and effects have been studied in dihydroquinoline type lipid soluble hypoxic radiation sensitizer (Sensorad), as well as in a water soluble radiation protector (DA) of well oxygenated mammalian tissues. Chemical parameters i.e. molecular weight, steric properties, functional groups of the recently developed new molecule have been reported pointing to the relationship of toxicity, distribution, absorption and elimination, as well as their bioavailability in the serum and tissues. As to the mechanism of action of hypoxic sensitizers comparison was performed with electron affinic compounds, with special emphasis on the in vivo formation of nitroxyl radicals. The action on DNA repair mechanisms has been given special attention. The DA has been compared with different radioprotective agents and its postirradiation protective effect has been stressed. Authors summerized the results of in vivo studies and animal experiments suggesting the possibility of the aimed planning of new compounds. Pathogenetic correlations of carcinogenesis, atherogenesis, xenobiotic induced organ injuries, radiation modificator effects and aging all involving free radicals have been discussed. The simultaneous use of the two compounds has been recommended.

COMBINED TREATMENT MODALITY IN STAGE III BREAST CANCER

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Among our breast cancer patients the rate of clinical stage III cases is very high, 25 - 30%. Bad prognosis was observed in this clinical stage in a previously study. Three year survival was 34.5% in this group.

The treatment problems of this stage are the following:

1. Primary tumour and RLN metastases are extended and fixed, 80% of the cases is regarded inoperable.
2. Chemotherapy is unable to control large infiltration. Temporary result is observed only in acut breast cancer.
3. The result with irradiation is good in 70% of the cases: total regression or partial regression are achieved. 30% of the cases do not respond well to irradiation.

In our institute the first choise of treatment is irradiation in stage III breast cancer. To improve the results of radiotherapy, we combine irradiation with MTDQ (a chemical radiosensitizer) and with Tamoxifen. Patients wee randomized into 3 groups:

1. Telecobalt irradiation + MTDQ (Sensorad)
2. Telecobalt irradiation + Tamoxifen
3. Telecobalt irradiation + Placebo

120 patients were treated with this protocol. The patients were checked and the results of the treatment were recorded 8 weeks after finishing the irradiation.

Comparing the results of Sensorad group to Placebo group, Sensorad patients showed better results. Concerning the Tamoxifen group, we need more cases for statistical analyses.

RAZOXANE (ICRF 159) AND RADIOTHERAPY IN THE TREATMENT OF ADVANCED SOFT TISSUE SARCOMAS. FIVE YEAR EXPERIENCE OF A RANDOMIZED STUDY

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The study was started in January 1978. All patients with histologically proven sarcomas of the soft tissues treated at the department of radio-oncology at the Medical School of Hannover were eligible to the trial. Since 1980 patients from the regional hospital in Feldkirch (Austria) have been included. Until 1983 eighty nine patients were randomized to receive radiation therapy alone or in combination with the sensitizing agent razoxane (ICRF 159). The protocol prescribed a total tissue dose of 60 Gy at a conventional fractionation for both groups. Dose reduction to 40 Gy was allowed and even recommended for retropertioneal disease and visceral metastases. Razoxane was given in a daily dose of 150 mg/m^2 per os beginning five days before the first radiation and continued during the radiation therapy. The report is restricted to the advanced cases, the results on postoperative therapy are too preliminary.

Among 56 patients with advanced inoperable disease 24 received radiation therapy alone. Twelf out of 24 (50%) showed a complete or partial response to radiotherapy. Of 32 patients receiving the combination of radiotherapy and razoxane 23 (72%) responded. The median survival in the two groups is as yet 12+ and 17+ months respectively. Considering the local control rates only (i.e. complete response as long the patient survives) the results in the combined treatment group seem to be comparable to those obtained with fast neutrons. The combined treatment with razoxane is associated with an acceptable degree of local and general toxicity.

TINIDAZOL AS RADIOSENSITIZER IN COMBINED TREATMENT OF CERVICAL CANCER

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During preoperative γ-irradiation, an agent Tinidazol (Polfa) was used as radiosensitizer at 2 g/m^2 of body surface in 32 patients with uterine cervix carcinoma. A single dose of 5 g was used to total 30 g. Tinidazol was taken four hours before 1, 3, 5 fractions of radiation. After 48 hours of irradiation an operation of extended panhysterectomy was performed. A morphologic study of ablated tumors was made. Data on the extent of expressibility of radiation changes in eliminated tumors, as compared to those in patients irradiated without radiosensitizing Tinidazol, served as criteria of the efficacy of radiotherapy.

CLINICAL TRIAL WITH FLAGYL (METRONIDAZOLE) IN CARCINOMA OF THE URINARY BLADDER

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Between 1979 and 1982 85 patients were randomized into adjuvant Flagyl (Metronidazole) or no adjuvant therapy. The basic treatment consisted of 20 times 2 Gy external megavoltage irradiation followed by simple cystectomy (category T3 and limited T4) or by a full course of external irradiation (70 Gy in 35 daily applications of 2 Gy). After randomization the adjuvant group receive Flagyl: during the first 3 weeks of radiation therapy 3 times weekly 6 g per square meter.

Clinical downstaging assessed after 4 weeks was comparable in the Flagyl- and the non-Flagyl-group. Pathological downstaging, which could be assessed in the cystectomy specimen of those undergoing cystectomy, was not related to additional Flagyl.
Three-year survival in the cystectomy group and in the full course of external irradiation group was not effected by additional Flagyl.

In the Flagyl group gastrointestinal toxicity (nausea and vomiting) afflicted 80% of the patients. Neurotoxicity expressed itself in the Flagyl group as headache in 37% of the cases, as dizziness in 17% and as peripheral neurotoxicity in 15%.

In view of the absence of any demonstrable beneficial impact of Flagyl, the trial was stopped.

INOPERABLE SQUAMOUS CARCINOMA OF THE BRONCHUS: IRRADIATED WITH OR WITHOUT METRONIDAZOLE AS A RADIOSENSITIZERS: A RANDOMIZED TRIAL

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A randomized controlled trial was undertaken in 3 different institutes in The Netherlands to evaluate the efficacy of metronidazole as a radiosensitizer in irradiating patients with inoperable squamous cell carcinoma of the bronchus. The study was initiated in 1980 and had to be stopped by mid 1982 due to increasing enthusiasm in treating the same group or patients with chemotherapy along with radiotherapy.

There are 54 patients in the study all of whom underwent split-course radiation therapy (3 Gy x 16 Fractions) with a pause of 2 weeks after 24 Gy in 2 weeks. The total TDF was 92. Half of these patients had metronidazole as radiosensitizer. They had 1.6 g/m^2 divided doses daily during the period of radiotherapy. No sensitizer was administered from the evening of Friday to Sunday-noon.

The tolerance to this treatment schedule was good with some gastro-intestinal toxicity and no peripheral neuropathy. Survival of the patients irradiated with radiosensitizer appears to be better, although a significant difference has not been achieved.

CHEMOPOTENTIATION PLUS RADIATION CURES A RESISTANT METASTASIZING SARCOMA

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Experiments were performed to design an effective combined modality therapy utilizing both interaction of agents in the primary tumor and spatial cooperation of agents against the metastases. Misonidazole (MISO) was evaluated in different three-agent treatment protocols combined with radiation and the nitrosourea 1-(2-chlorethyl)-3-cychohexyl-1-nitrosourea (CCNU). The protocols were designed to maximize both the chemopotentiating and radiosensitizing properties of MISO. For these studies, the KHT mouse sarcoma was chosen because, in this tumor model, tumor-free survival is possible only when both the primary tumor and secondary metastases are effectively managed. We had previously shown that MISO markedly enhances response to CCNU in primary KHT tumors as well as secondary lung metastases.

Radiation was delivered to the tumor region of the legs of non-anesthetized female C3H/HeJ mice. MISO and CCNU were injected intraperitoneally. MISO was administered 30 - 40 min prior to radiotherapy and simultaneously with CCNU except in the CCNU-MISO timing studies. Tumor response was assessed by in situ tumor growth delay or by determining the number of animals surviving tumor-free for 100 days after treatment.

In initial experiments mice were injected with 1.0 mg/g of MISO simultaneously with a 20 mg/kg dose of CCNU 30 - 40 min prior to irradiation with 15 Gy. This protocol produced 60% tumor-free mice 100 days post treatment. By comparison all two agent combinations produced no tumor cures. The relative importance of chemopotentiation versus radiosensitization was determined by treating with MISO plus either radiation or CCNU and then at times ranging from 0 - 24 hr later treating with the other agent. When the time between treatments was 0 - 6 hr, 60 - 80% tumor control was achieved for both MISO plus radiation followed by CCNU and MISO plus CCNU followed by radiation. However, if the time interval was increased to 18 or 24 hr, the cure rate in the former protocol dropped to 10%, while that of the latter remained high at 40%. These good results were due mainly to the chemopotentiating effect when CCNU was given 0 - 6 hr after the MISO-radiation combination and did not result from effects of radiation-CCNU sequencing. This chemopotentiation was lost when MISO was administered 18 to 24 hr after the radiation - MISO treatment and consequently the data at these time

intervals reflect the effect of radiosensitization only. Other experiments to evaluate complete dose response curves for tumors and some critical normal tissues have been initiated or completed. These include regimens where MISO is administered at clinically achievable levels and with simulated human pharmacokinetics. These recent experiments and other results from our laboratory, indicate that chemopotentiation combined with radiation can be a very effective therapy for some tumors where control of both local and metastatic disease is necessary for treatment success.

MISONIDAZOLE AND HIGH-DOSE IRRADIATION IN THE TREATMENT OF GLIOBLASTOMA MULTIFORME: FINAL REPORT

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In a randomized study, investigating the hypoxic cell sensitizer misonidazole, 52 patients with high-grade astrocytomas were referred for postoperative radiotherapy to the University Clinic for Radiotherapy and Radiobiology of Vienna. With a medium follow-up of 5,5 years, 50 patients were available for analysis. All patients received the same radiation treatment (66,5 Gy in 31 fractions over 7,5 weeks, field size reduction after 45 Gy). In the first, second and eighth week a 4 Gy tumor dose was given on Monday and Thursday. Misonidazole was given 4 hours before irradiation to 21 randomized patients on those 6 treatment days (2,1 - 2,7 g/m^2 per treatment day). Daily tumor doses of 1,7 Gy were administered ')nday through Friday from the third until the seventh week. Median survival was 9,6 months for patients treated with irradiation alone and 12,0 months for patients with misonidazole-sensitized irradiation. The corresponding 1-year survival rates are 34% and 43%, respectively. There is no statistically significant difference between the treatment groups. The extend of surgery and the age of the patients were observed as highly significant prognostic factors. Median survival of patients with radical and subtotal operations is 15,5 and 6,8 months, respectively. Younger patients had a better medium survival than elderly (18 months vs. 8 months). The Cox regression analysis shows no influence of sex, histological grade, performance status and tumor localisation. Neurotoxic side effects of misonidazole were minimal.

MISONIDAZOLE COMBINED WITH SPLIT-COURSE RADIOTHERAPY IN THE TREATMENT OF INVASIVE CARCINOMA OF LARYNX AND PHARYNX

The Danish Head and Neck Cancer Study Protocol 2

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The DAHANCA 2 protocol includes all eligible Danish pharynx and larynx carcinoma patients (except larynx stage 1). Patients are randomised to 2 different split-course radiation regimes and are given either misonidazole (MISO) or placebo (11 g/m^2) during the initial 4 weeks of treatment.

The study was initiated in October 1979. Per May 1984 have 554 patients been included. An analysis of the first 494 patients (386 males, 108 females) showed that females had a statistically better local/regional control (52% vs 38%, 4 years actuarial value). Overall the MISO treated group had a 7% better local control rate than the placebo group. This effect was not found among females, whereas males had a 10% improvement in favour of MISO. This difference was only found in patients with supraglottic and pharynx carcinomas (39% vs 25%). Especially in pharynx tumors was the difference statistically significant in all stages (overall disease free rate: 46% vs 26%, P 0.02), and this benefit of MISO was also found in the 3 year crude survival rate (53% vs 37%). Also the preirradiation hemoglobin concentration was found to be an very important prognostic parameter. In females the local control were 38% and 57% respectively in patients with hb values below or above 8 mmol/l. In males the same values were 30% and 44% below or above 9 mmol/l. The hb effect was most pronounced in advanced stages, and a high hb level tended to improve the MISO effect. Thus in the male pharynx group placebo patients with low hb had a 14% disease free rate compared to 61% in MISO patients with hb 9 mmol/l.

MISO induced peripheral neuropathy in 29% of the MISO treated patients. The incidence and severity of the neuropathy depended on the total dose and the plasma pharmacokinetic parameters. Among the latter the area under the curve (AUC) was found to be the most predictive for the occurrence of neuropathy. Currently dose reduction is done in patients with high AUC. This reduces the toxicity to about 10%.

PARTICLE-BEAM

THERAPY

Friday, March 29, 1985

AN UPDATE ON RESULTS OF RADIOTHERAPY WITH HEAVY IONS

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A clinical trial of helium and heavier charged particle has been carried out at Lawrence Berkeley Laboratory with the assistance of the Northern Californa Group and the Radiation Therapy Oncology Group. Over 700 patients have been entered in these trials which have largely been Phase I and II studies with helium, carbon, neon and silicon ions. Companion biophysical studies have been carried out to characterize the RBE, OER, cell cycle kinetics, acute and chronic tissue effects, tumor biology as well as basic molecular and track structure effects of heavy ions. Improvements in beam delivery should shortly lead to use of magnetically spread beams with larger, flatter fields and less fragmentation. Refinements in treatment planning and delivery have lead to improved patient positioning and immobilization, better compensation for tissue inhomogeneities and more accurate isodose calculations, both for physical and biologically modified treatment plans. Magnetic resonance imaging has been introduced into treatment planning and follow up. Heavy charged particles have been found to be extremely valuable for irradiation of unresectable lesions close to critical structures such as spinal cord and base of brain. Local control rates in such lesions appear to be around 80% while upwards of 95% of uveal melanomata appear controlled. Selected head and neck tumors and localized soft tissue sarcomata also appear to show advantageous therapy with heavy charged particles. With more difficult, larger tumors such as carcinoma of the pancreas or glioma of the brain, only modest success has been seen. Phase III studies with neon heavy charged particles are planned in unresectable carcinoma of the lung (non small cell) and locally advanced carcinoma of the prostate. Further Phase I-II studies are needed before silicon heavy particles can be evaluated prospectively. Target sites under consideration for silicon include head and neck tumors, soft tissue sarcoma and possibly brain tumors.

PRACTICAL PROBLEMS RELATED TO NEUTRON RBE IN NEUTRON THERAPY

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Neutron RBE depends on neutron energy, but also on dose per fraction, biological system or effect, and experimental conditions. However, when transferring clinical information from a neutrontherapy centre to another one, a single factor is in general sufficient to take into account the RBE differences between the two neutron beams (Clinical Neutron Intercomparison Factor or CNIF).

The problem is more complex when neutron doses an photon doses have to be compared. In practical situations (e.g. preparation of a new protocol or mixed-schedule irradiation), a single conversion factor has sometimes to be selected and adopted to take into account the neutron RBE. The "Clinical Neutron Potency Factor" (CNPF) can be defined as the ratio of the total γ-dose and the total neutron dose corresponding to the late tolerance of normal tissues (fibrosis/necrosis). The CNPF varies from Centre to Centre, depending on neutron energy but also on the fractionation schemes adopted for photons and neutrons.

As an alternative, the CNPF could be defined as the ratio of the toal tolerance doses for photons and neutrons, derived from clinical experience, in a given centre, for a given tumour localization. In the first approach, the CNPF can be obtained from pure radiobiological experiments; the second approach implies addiational clinical jugdment. The clinical tolerance dose depends on beam penetration, but with the high energy neutron beams recently introduced in neutrontherapy, both approaches become closer and closer, since dose distributions become similar for high-energy photons and neutrons.

IMPROVED TREATMENT TECHNIQUES FOR 14 MeV NEUTRONS

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The neutron source which is in use at the German Cancer Research Center is the high power d-t closed system neutron generator tube KARIN. The use of monoenergetic 14 MeV neutrons from the T(d,n) reaction gives a depth dose distribution which corresponds approximately to the dose distribution of Co-60 gamma rays.

But there are some disadvantages namely the wide pneumbra, no clinical observed skin sparing, an additional inhomogeneity problem, due the atomic composition of tissue and some technical problems. Using treatment techniques known from Co-60 therapy may result in unexceptable treatment plans for neutrons.

In the future high energy cyclotrons producing neutrons that show dose distributions similar to high energy protons will overcome some of these disadvantages. On the other side 14 MeV neutrons can be used as a cheap alternative.

The above mentioned problems may be solved by improved treatment techniques. We have developed a simple form of computer controlled dynamic treatment technique for fast neutrons. It can be shown, that qualitativ equal treatment plans for Co-60 and 14 MeV neutrons are possible, but for neutrons more intricated techniques are necessary.

BARON-LABELLED IMMUNE-BODIES. PRECLINICAL STUDIES

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Abstract not arrived by deadline.

COMBINED ACTION OF THERMAL NEUTRON IRRADIATION AND A BORON-10-CLYCINE-AMIDE-ANALOG ON A SOLID EXPERIMENTAL TUMOR (EO 771)

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If a tumor can be preferentially loaded with a suitable ^{10}B-compound and irradiated with thermal neutrons, malignant cells can be selcetively destroyed via the reaction $^{10}B(n,\alpha)^{7}Li$; both the α particle and the Li nucleus have a high LET and an OER of about 1; the two particles combined have a range of about 14 /um in soft tissue.

Neutron capture with two boron-10-aminoacid-analogs with 90% enriched Boron-10 of low toxicity was tested in the past: (a) Trimethylamine-carboxyborane (A3), (Mol weight: 116.2) and (b) Amine-carboxyborane (A7), (Mol weight: 74.1). Now the boron-10-glycineamide-analog (A8), with 90% enriched Boron-10, Amineborylcarboxyamide (Mol weight: 73.19) was synthesized; it contains 13.81% Boron and shows a very low toxicity in mice.

Effects of this compound were tested on the syngeneic solid adenocarcinoma EO 771 (diameter 8 - 9 mm) on the right hind leg of male C57 BL/6J mice, by measuring tumor growth delay and cell cycle changes using flow cytometry. This tumor is known for its high radioresistance, needing 40 Gy local Co60- γ - irradiation for a growth delay of 5 days. Boron distribution between tumor and muscle were analysed by emission spectroscopy with inductive coupled plasma (ICP) following injection of peanut oil emulsin, which gave the highest tumor concentration at 30 min after intratumoral injection.

The tumors were exposed to thermal neutrons (flux $2.2 \cdot 10^{10}$n/cm^2 sec; Cd-ratio 100) in a thermal column of the 10 MW-swimming pool reactor FRJ-1; the bodies were shielded by a small boron carbide plastic container. The tumors were irradiated 30 min after A8 injection.

Boron 10 concentration in the tumors at time of irradiation was 70 /ug/g after intratumoral injection of 1.0 mg A8 dispersed in 0.1 ml peanut oil emulsion.

Neutron irradiation with $1 \cdot 10^{12}$ - $4 \cdot 10^{12}$n/cm^2 alone produced a growth delay of 1 - 2 days.

A8 plus $1 \cdot 10^{12}$n/cm^2 neutrons resulted in a growth delay of 1.5 days and increase of fraction of (G2 + M) cells from 35 - 40% (neutrons alone) to 40 - 45%.

A8 plus $4 \cdot 10^{12}$n/cm^2 neutrons gave a growth delay of 6.5 days; the fraction of (G2 + M) cells rose to 55 - 65% and the absorbed tumor dose from α particles from A8 was about 33 Gy.

The results show that the concentration of A8 in tumors distinctly enhanced the effect of thermal neutron on growth delay and produced a partial cell accumulation in (G2 + M) phase of the cell cycle, despite the high radioresistance of this tumor.

CLINICAL RESULTS WITH FAST NEUTRON-THERAPY (DT, 14 MeV) SINCE 1976 IN HAMBURG-EPPENDORF

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Between 1976 and 1980 we irradiated 328 patients with different types of tumors. After successful technical improvements concerning dose-rate, reliability and economy we are again treating patients since January 1984.
Analysis of early and late effects of fast neutrons only (up to 16 Gy/4 weeks) or therapy with mixed photon-neutron-schedules on tumors and normal tissues. Comparison with the results in other centers and outlook in future programs.

NEUTRON- AND NEUTRON-BOOST-IRRADIATION OF SOFT TISSUE SARCOMAS

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The majority of soft tissue sarcomas are slowly growing, differentiated tumours with long volume doubling times. The biological reasons for treating these tumours with high LET radiation qualities are:

1) a reduced oxygen enhancement ratio (OER)
2) a differential sensitivity in G1 phase of the cell cycle
3) a reduced capacity for repair of potentially lethal damage

In preliminary reports, high local control rates of 69 - 75% have been reported by several authors for neutron irradiation of gross tumours (Caterall & Bewley, 1979; Franke, 1979; Salinas et al., 1980). However, the late morbidity rate of 28 - 40%, which was reported by some investigators, was considered unacceptable.

Up to now we have treated 260 patients with soft tissue sarcomas. The results of 199 patients who were treated between 1978 and 1983 are presented in this report. The mean follow-up period is 42 months with a range of 12 to 66 months.
Two groups of patients are distinguished:

1) patients without clinical evidence of residual tumour at the beginnung of radiotherapy after previous surgery,
2) patients with gross tumour at the beginning of radiotherapy

The actuarial survival rate at 6 years for the first group of patients is 63,6%, compared to 30.9% for the second group ($p = 0.002$; Gehan-Wilcoxon-Test).

Further differences in local control rates at last review were found as a function of tumour stage, i.e. 93% for T1 tumours (UICC Classification, Geneva, 1978), 87% for T2 tumours and 73% for T3 tumours. Comparable control rates have not been contributed to date for photon and/or electron irradiation mainly for T3 tumours.

The corresponding actuarial survival rates at 6 years are 77% for T1 tumours, 63,1% for T2 tumours and 34% for T3 tumours. the rate of serious complications is 18% for patients with no clinical evidence of tumour ($N = 107$) and 30% for patients with gross tumour ($n = 92$).

Our five year recurrence free actuarial survival rate for patients with T1 and T2 tumours is 59%, compared with a weighted average of 41% in historical series.

The rather high overall morbidity rate of 22% after a full neutron treatment was reduced to 15% after the introduction of a neutron boost. At the present time, the results of this modified treatment are not inferior to a full neutron course.

This combined method using a neutron boost will be compared with postoperative photon and/or electron irradiation in a prospective EORTC trial.

FAST NEUTRON THERAPY AT NIRS

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The effect of fast neutrons in the treatment of locally advanced cancers was evaluated.

The results show that local control rate of the tumor has been improved by applying fast neutrons, especially in the treatment of carcinoma of the larynx, Pancoast' tumor of the lung, carcinoma of the esophagus and osteosarcoma. For carcinoma arising from the supraglottic region, the rate of local control was 69.2% in the cases treatet with fast neutrons, whereas the rate was decreased to 37.6% in the photon beam series. In the treatment of carcinoma of the esophagus, Pancoast' tumor and osteosarcoma, the improvement of local control obtained by fast neutron therapy has been rewarded by good survival rates.

The results also suggest that fast neutrons will be useful in the case of preoperative irradiation for carcinoma of the urinary bladder and soft tissue carcinoma.

The rate of down stage of carcinoma of the urinary bladder was observed more markedly following fast neutron irradiation compared with the case of photon beam irradiation. Local recurrence of soft tissue sarcoma seemed to be decreased when fast neutrons were used before surgery.

Based on the clinical trials with fast neutrons and protons, a project study with accelerated heavy ions is planning at NIRS.

VALUE OF HIGH LET (NEUTRON) AND LOW LET (X-RAY, Co-60) RADIATION THERAPY IN PAROTID MALIGNANCIES: A COMPARATIVE STUDY

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In a patient group with parotid tumors 15 persons received fast neutron therapy and 106 conventional radiation therapy. The therapeutic results were referred to the local control rate. The following conclusions were drawn:

Both radiation therapy qualities accounted for a practically identical recover rate of the small tumors (St. I-II), but neutron therapy was more efficient in advanced cases (St. III-IV).

Side symptoms (necrosis) were shown by two patients given neutron therapy, but did not occur in any case of conventional radiation therapy.

We therefore recommend conventional radiation therapy for small tumors (St. I-II) of the parotid gland, and neutron therapy for advanced (St. III-IV) tumors thereof, since in the latter cases neutron radiation is more efficient despite occasional side effects.

FAST NEUTRON THERAPY OF HEAD AND NECK CANCER: THE RTOG EXPERIENCE

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Between 1977 and 1984, the Radiation Therapy Oncology Group carried out three prospective, randomized studies of fast neutron and mixed beam (2/5 neutron and 3/5 photon) radiation therapy in head and neck cancer. Patients with unresectable squamous cell carcinomas and unresectable salivary gland tumors were studied.

Three hundred twenty-two patients with squamous cell carcinomas of the head and neck were entered on a study testing mixed beam radiation therapy against photon radiation therapy. One hundred forty-five patients were randomized to treatment with photons, and 177 patients were randomized to treatment with mixed beam radiations. The randomization was purposefully unbalanced in favor of the experimental treatment. No significant overall advantages could be demonstrated for mixed beam treatment over photons for either local tumor control or survival.

Forty patients with advanced, unresectable squamous cell carcinomas of the head and neck were entered on a study comparing high energy (35 MeV d– Be and 66 MeV p– Be) neutrons against photon radiation therapy. The complete response rate for the neutron-treated group was 52%. The complete response rate for the photon treated group was 17%. The difference ist statistically significant at the $p = 0.03$ level. The two-year survival rates for the neutron-treated group and the photon-treated group were 25% and 0% respectively. The major complication rates were not statistically significantly different for the two groups (18% for neutrons and 33% for photons).

Twenty patients with salivary gland tumors were randomized to receive photon or neutron radiation therapy. The local tumor control rates were 86% for neutrons vs 14% for photons. At this time, there is no significant survival advantage for the neutron-treated group, although there is in advantage in disease-free survival.

FAST NEUTRON RADIOTHERAPY FOR ADVANCED CARCINOMAS OF THE URINARY BLADDER AND PROSTATE GLAND: RESULTS OF RTOG CLINICAL TRIALS

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Between 1977 and 1983 the Radiation Oncology Study Group (RTOG) carried out two studies testing the efficacy of fast neutron radiotherapy for advanced malignancies of the genitourinary tract. Because of the limited depth-dose characteristics of the relatively low energy beams that were then available, patients were treated with a "mixed beam" schedule consisting of 2 neutron and 3 photon treatments per week (approximately equal biologically daily doses).

Patients entered on the bladder study had stage B_1 (grade III or IV histology) or stage B_2, C, or D_1 (any grade histology). Thirteen patients received preoperative mixed beam irradiation to 50 Gy-equivalent followed by cystectomy. The incidence of pathological downstaging to P_0 was 58% in the cystectomy specimens (compared with 25 - 35% expected for similar groups of photon treated patients). Twenty-six patients were treated definitively with 50 Gy-equivalent to the pelvis followed by a 20 Gy-equivalent ooost to the bladder. 18/26 (69%) achieved tumor clearance at some point in their followup, but 8/18 (44%) of these ultimately exhibited some degree of local failure. The survival at 30 months for this group of patients was ~34%, but the subgroup of patients with stage B and C disease had a projected survival of ~60%.

Patients entered on the prostate study had stage C disease and were randomized to receive either definitive mixed beam or photon irradiation consisting of 50 Gy-equivalent to the pelvis followed by a 20 Gy-equivalent boost to the prostate. The randomization was purposefully unbalanced (60 - 40%) in favor of the experimental treatment, with 53 evaluable patients entered on the mixed beam arm and 36 evaluable patients entered on the photon control arm. The two patient groups are balanced in regards to degree of tumor differentiation, prior hormonal therapy status, Karnofsky performance status, and serum acid phosphatase levels. Gleason grading of the lesions is currently being carried out. Actuarial survival curves indicate a definitite survival difference in favor of the mixed beam subgroup. At 60+ months from completion of treatment, ~70% of the mixed beam subgroup are still alive compared with ~25% of the photon treated patients. This difference is statistically significant at the $p = 0.01$ level. Local control and time to the development of distant metastases are currently being evaluated. A comparison will be made with the results of other RTOG photon studies for stage C prostate cancer.

For both tumor systems treatment related morbidity appears comparable with that expected for comparable groups of patients treated with photon irradiation.

DEVELOPMENT AND IMPLEMENTATION OF PROTON RADIOTHERAPY AT THE GUSTAF WERNER INSTITUTE. EXPERIENCES AND PLANS

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The 230-cm cyclotron at the Gustaf Werner Institute is located at a distance of 1 kilometer from the Department of Oncology of the University Hospital in Uppsala. This situation formed a suitable prerequisite for clinical tests with a 185 MeV proton beam in the years 1957 - 1968. For practical reasons - the radiotherapeutic research was conducted as part of an extensive research programme in physics, chemistry, biology and medicine - only small series of patients were treated. It was decided to postpone a continuation of the programme until the completion of a major reconstruction of the cyclotron and the radiation laboratory.

The reconstruction will turn the former synchrocyclotron into a modern hybrid accelerator - a combination of a sector-focussing and frequency-modulated cyclotron. The first beams are expected to appear in the rectonstructed radiotherapy rooms in the beginning of 1986. In this situation it is of interest to summarize the experiences gathered with the old accelerator and to discuss the plans which are presently being established for the new facility. The paper is divided in three parts.

1. A brief review of the experiences from the activities 1957 - 1968.
2. An outline of the new facility.
3. A presentation of the plans for the new facility in Uppsala.

The discussion will be focussed on the choice of patients with a view towards the scientific and clinical inquiry. Two alternative solutions for the beam transport system will be presented and discussed from the point of view of clinical nerits, technical problems and the international situation in particle radiotherapy.

THREE YEARS OF CLINICAL EXPERIENCE WITH DYNAMIC PION THERAPY

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The paper will review the methods and results of pion therapy using the spot scanning technique in over 120 cases treated 1982 - 1984. The data will emphasize the relationships of dose and treatment volume to normal tissue reactions and tumor control with description of methods to achieve optimization.

The various sites treated include brain, biliary tract, pancreas, uterus, rectum, bladders and connective tissues. Certain sites and histologies appear more favorable to pions than others. Analysis of reasons for this will also be presented with reference also to Los Alamos and Vancouver data.

OPTIMIZING COMBINATIONS

OF RADIOTHERAPY AND OTHER

THERAPIES

Saturday, March 30, 1985

THE ROLE OF RADIOTHERAPY IN THE COMBINED MODALITY TREATMENT OF SMALL CELL BRONCHUS CARCINOMA

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The use of thoracic irradiation as an additional adjunct in controlling local disease in SCLC has shown conflicting results in prospective trials comparing systemic chemotherapy alone versus chemotherapy plus thoracic irradiation.

Modern aggressive chemotherapy regimens have led to improvements in survival-time of SCLC over the past decade, it has become appearant that the frequency of brain metastases increases with the duration of survival. In randomized trials prophylactic cranial irradiation (PCI) was associated with a reduction of clinical detection of brain metastases from 20% to 6%. However, there was no significant impact on survival. Results appear to confirm that only complete responders to systemic chemotherapy have the potential for survival benefit from PCI, and that the magnitude of such a benefit, if it exists, is not great.

First results of a new protocol activated by the Viennese Lung Working Group with international cooperation would be discussed regarding the role of radiotherapy, surgery and chemotherapy.

IMMUNOMODULATORY AND MEMBRANE PROTECTIVE EFFECT OF NEW DIHYDROQUINOLINE TYPE ANTIOXIDANTS

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The authors have been studied the effect of different radical scavangers (cyanidanol-3, dihydroquinoline type synthetic antioxidants, aicaphosphate, etc.) on the immune reaction. The immunological effects of these drugs were tested both by several in vitro methods of lymphocyte cultures and by in vivo models of experimental animals. The radical scavanger activity was investigated by the methods for lipid peroxidation and also by the release of beta-glucuronidase from the lysosomes. These drugs differently inhibit the lipid peroxidation and they have a membrane stabilizing effect. These effects could be demonstrated on plasma membrane and on microsomal fractions of brain and liver as well as on liver lysosomes in experimental animals. The immunomodulatory effects of these drugs are different. In some tests they exert immunostimulant, in others they do immunosuppressive effect. On the basis of the in vitro data the most convenient drug can be chosen for the adjuvant therapy of patients treated with cytostatics or radiotherapy.

HUMAN LEUKOCYTE INTERFERON AS PART OF A COMBINED TREATMENT FOR PREVIOUSLY UNTREATED SMALL CELL LUNG CANCER

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Human leukocyte interferon, HuIFN-α(Le) has been tested in combination with radiotherapy and chemotherapy for previously untreated small cell lung cancer. Nine patients with limited disease received high-dose IFN followed by a low-dose regimen; and six patients had a low-dose regimen from the beginning. The high dosage of IFN consisted of 800 x 10^6 IU given as a continuous iv. infusion during 5 days, followed by 6 x 10^6 IU im. 3 times weekly. If the first site of disease progression was local or a CNS location, radiotherapy (55 Gy/20 F/7 wk locally and/or 30 Gy/10 F/2 wk whole brain) was applied and IFN was continued. Chemotherapy was administered only at disease dissemination outside the chest. Three patients achieved minor response for as long as 20, 25 and 42 weeks, respectively, with IFN alone. Three of 5 complete responders to IFN-radiotherapy died 18, 33 and 41 wk from the start of IFN without chemotherapy. Autopsy did not reveal any macroscopic or microscopic tumor at any site but severe radiation pneumonitis. Four out of 9 patients were administered chemotherapy subsequent to IFN-radiotherapy by reason of disease dissemination. The median survival of the entire group was 41 wk. On the low-dose regimen, one patient achieved partial response of IFN alone, duration 12 wk, of 5 evaluable patients 3 achieved CR and 2 PR to IFN-radiotherapy, and one of the 3 complete responders to IFN-radiotherapy died of severe radiation pneumonitis at 21 wk from the start of IFN. No tumor was detected at autopsy. The study is in progress. Average survival at present is 33 wk. The results derived from both our studies may suggest a growth-delaying effect of HuIFN-α(Le) on small cell lung cancer. They also suggest potentiation of radiation by HuIFN-α(Le). Memory and psychomotor dysfunction, fatigue and anorexia were dose-limiting with both short-duration high-dose, and long-duration low-dose IFN therapy. We feel that IFN as part of a combined multimodality treatment of small cell lung cancer may play a role by delaying metastatic dissemination.

OPTIMIZING COMBINATIONS OF ALTERNATING RADIOTHERAPY AND CHEMOTHERAPY IN LIMITED SMALL CELL LUNG CANCER

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Alternating radiotherapy (RT) and chemotherapy (CT) schedules were designed to deliver relatively high dose radiotherapy in 3 courses alternating with combination chemotherapy in order to maximize both local control and long term survival. Thirty-five patients with limited disease entered in a second protocol concerning small cell lung carcinoma (SCLC) from November 1981 to December 1982. This protcol is still on going. Six cycles of induction CT were given according to this schedule: Doxorubicin 40 mg/m^2 d1, VP16213 75 mg/m^2 d1-3, Cyclophosphamide 3oo mg/m^2 d3-6, CDDP 100 mg/m^2 d2. Thoracic RT was delivered in 2 courses of 20 Gy in 8 fractions and 14 days, the third course of RT delivered 15 Gy in 6 fractions by lateral fields. Prophylactic brain RT was given during the first course of thoracic RT. The alternating schedule can be summarized as follows: 2 CT-RT-CT-RT-CT-RT-2 CT. One week gap was respected between RT und CT. Patients in CR received 8 cycles of maintenance chemotherapy.

This protocal proved to be feasible; early toxicity and late complication rates were considered as acceptable. Therapeutic results can be summarized as follows: CR rate after the induction treatment: 91%. Actuarial local control rate at 2 years: 82%. Actuarial relapse free survival at 2 years: 34%. Median overall survival: 20 months.

Because the high percentage of CR we are using this protocol as our standard induction regimen. In conclusion, the alternating schedule deserves to be further investigated using different combinations of CT, radiation doses and new approaches in maintenance therapy.

LATE EFFECTS OF COMBINED CHEMOTHERAPY AND RADIOTHERAPY IN THE GASTROINTESTINAL TRACT

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The safety of multimodality therapy cannot be predicted by how well it is tolerated initially. Danjoux reported 24 patients with rectal carcinoma who were treated by a split-course irradiation and 5-FU. The acute reaction was minimal but 7 of 24 patients (29%) developed serious complications about 8 months following treatment. The serious complications consisted of bowel stenosis, necrosis, fistula formation and subcutaneous fibrosis. Ransom reported that 6 of 16 children treated with simultaneous drug-radiation therapy for abdominal rhabdomyosarcoma developed severe small bowel complications resulting in death in three cases. From 1978 -1981 38 patients with stage III ovarian cancer were treated with chemo-radiotherapy and maintenance chemotherapy at the University Clinic for Radiotherapy and Radiobiology in Vienna. 4 of the 38 patients required surgery for bowel obstruction 7 - 11 months after irradiation and were found tumor free at that time. These late complications may be a result of the interaction of radiation and drugs and could be explained by the concept of stem cell senescence. With fractioned radiation to tolerance, the microcirculation is altered, but no late effects occur until another challenge is made to the organ system. Maintenance chemotherapy is well tolerated initially but uses up crypt stem cell regenerative reserve. By chemotherapy and radiotherapy acting on different populations of cells an enhanced effect is encountered.

RADIOTHERAPY COMBINED WITH INTRAARTERIAL CHEMOTHERAPIE IN ADVANCED TUMORS OF THE UTERINE CERVIX

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During the last four years nearly twenty patients have undergone long term intraarterial chemotherapy because of advanced cancer of the uterine collum.

Method:

After the punction of the arteria femoralis according to Seldinger's technic we drive a normal arteriagraphic catheter into the arteriae hypogastricae, possibly under the level of the origin of the arteria glutealis superior. Having fixed the catheter in this position or after changing for a more suitable thin teflon catheter we administer drugs intraarterially through a longer period: 1 - 4 weeks.

This combined chemotherapy (usually two drug protocoll) will be carried out two times a week. The time of the drug administration depends on its kinetics but usually we administer the desired volume of drug in six hours. After each drug administration we give a percutan irradiation (cobalt 60 teletherapy), usually 3500 -4000 cGys.

Patients:

First of all young patients were involved into this treatment protocoll partly because of the increased risk, partly because of possible complications. In a part of this patients the combined chemoradiotherapy was the last step in their treatment. All the patients were in the stage III-IV.

Results:

All the patients have responded, but only a few complete remissions were detected. One patient has have a complete remission, histologically prooved and some tumors became technically operable.

Complications:

This type of the long term intraarterial chemotherapy requires a very good patient care, but dispite this, more or less serious complications are to be expected, due to the long term cannulation of the arteria femoralis. We have had two occlusion of the arteria femoralis (one only transient). Neither of them required surgical intervention. In some cases we had a circumscribed skin reaction of bleomycin. During the therapy we have had one death due to ultiplex pulmonary embolism which might have its origin of the venous plexus of the true pelvis, according to autopsy.

Discussion:

Intraarterial chemotherapy seems to be more effective in cervix cancer than generally administered chemotherapy.

Selective cannulation of the required arteria does not make any problem.

Danger of the long term intraarterial cannulation can and must be decreased by more advanced technic.

TREATMENT OF ADVANCED OVARIAN CARCINOMA BY CHEMOTHERAPY WITH CIS-PLATINUM, ADRIAMYCIN AND CYCLOPHOSPHAMIDE (CAP), SECOND LOOK OPERATION AND WHOLE ABDOMINAL IRRADIATION

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The introduction of new irradiation techniques and aggressive combination chemotherapy has undoubtedly improved the poor prognosis of advanced ovarian carcinoma. While the resu'ts of combination chemotherapy increasingly favour the schemes including cis-platinum, the necessary duration of therapy and the best procedure following the accievement of complete remission have not yet been clearly established.

A new therapy concept has been introduced by the Tumorzentrum Munich, in which several institutions are participating. Following a complete remission after CAP and second look operation the patients are concidered to receive whole abdominal (moving strip) irradiation. Up to May 1984 30 patients have been included in this scheme (observation time since first operation 8 - 36 months). The preliminary results show that whole abdominal irradiation can be performed after aggressive chemotherapy and second look operation and that it is well tolerated. The patients where surgical debulking was primarily possible or the patients where complete remission was accieved following the second operation seem to benefit the most from the combined therapy. Patients who still had active tumor in the upper abdomen (infiltration of omentum), at the time of the second look operation, even though this could be macroscopically completely removed, tend to relapse dispite the whole abdominal irradiation.

The study continous. In March 1985 we hope to be able to report on 40 - 50 cases who will have been treated within this programme (observation time since first operation 8 - 45 month).

RADIOTHERAPY AND OTHER THERAPIES,

INCLUDING SURGERY

Saturday, March 30, 1985

THE 50 GY-EFFECT: KEY TO AVOID MUTILATING SURGERY IN THE TREATMENT OF HEAD AND NECK CANCER?

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Therapy generally starts with an irradiation (RT) of the primary and the entire cervical lymphatic drainage, the latter with exception of $T_{1-2}N_0$ glottic CA. After 50 Gy depending on tumor type, stage, reaction of tumor and normal tissues as well as operability, a joint conference determines which of the following 3 strategies is to be followed:

1. RT up to a curative dose, in N_0 restricted to the primary, in N_1 smaller than 2 cm responding well to 50 Gy also to involved nodes. 2. Curative tumor dose only to the primary, conservative neck dissection for lymph nodes larger than 2 cm or smaller nodes without satisfactory regression. 3. Termination of RT followed by radical surgery of the primary and, depending on the lymph node situation, combined with conservative neck dissection.

Between 1/1/72 and 12/31/80 310 consecutive patients with CA of the larynx (n = 143), oro- (n = 71) and hypopharynx (n = 39) as well as of the oral cavity (n = 57) have been treated. In 243 (78%) cases, therapy started off with RT. In 165 patients this was the only curative measure, in 44 cases a preoperative and in 34 a palliative procedure. 60 (19%) patients were primarily operated on with aim at cure, 33 of them received postoperative RT.

The actuarial 5 year disease free survival is 97, 72, 60, 63 and 42% for stage T_1N_0, T_2N_0, T_3N_0, T_4N_0 and $T_{1-4}N_1$ laryngeal CA, 68, 49 and 40% for stage $T_{1-2}N_0$, $T_{1-3}N_1$ and $T_{1-4}N_{2-3}$ CA of the oropharynx, 68 and 43% for stage $T_{1-3}N_0$ and $T_{1-3}N_1$ CA of the hypopharynx and 80, 56, 44 and 43% for stage $T_{1-2}N_0$, T_3N_0, $T_{1-3}N_1$ and $T_{1-3}N_{2-3}$ CA of the oral cavity. - These results suggest that cure can be achieved in a large proportion of cases without sacrificing function.

For the presentation our experience will be updated to December 12, 1983. Since our treatment programme has continued unchanged, the number of patients analyzed will be correspondingly larger, with a medium follow up time of greater than 5 years.

RESULTS OF CT-GUIDED STEREOTACTIC CURIETHERAPY OF MIDLINE TUMORS OF THE BRAIN

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From a total of 1.157 stereotactic treated tumor cases followed up, 365 midline space occupying processes (hypothalamus, midbrain, lower brainstem) were biopsied between 1965 - 1983. 1971 were irradiated with I-125 or Ir-192 interstitially. 37 intratumoral cysts were drainaged by a Rickham-Catheter. The best chances of survival showed the low graded gliomas of the upper midline area, whereas the benign lesions of the pontine region gives only for the elder patients a good chance. An external irradiation of the midline area should be taken out after a histological verification of the lesions. This is pointed out by the fact, that 8,5% of our cases are nontumoreous processes such as a hemorrhage, glioses or abscesses.
A detailed report of our results is given and therapeutic consequences are discussed.

NEW TREATMENT MODALITIES OF COMBINED RADIOTHERAPY AND SURGERY IN ADVANCED CARCINOMAS OF THE UPPER JAW

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Four cases are presented where the tumor had destroyed the base of the skull. A primary resection of the tumor was not indicated and only in those cases where the actual extension of the tumor could not be realized by diagnostic methods as CT, endoscopy and X-ray the operation was the first step. Therefore different treatment modalities have to be used. In three cases the tumor was first radiated in order to enable the consecutive operation. The radiations were applied in a split-course with sensitizers or chemotherapy. In one case the radiation was carried out postoperatively, because it was not possible to remove the tumor from the base of the skull in a radical manner. In all cases the tumor could be controlled or total tumor regression was achieved. The first step of treatment gives the second the chance to controll the tumor. Surgery or radiotherapy alone is condemned to fail. One patient died two years later of mediastinal metastasis, but no tumor could be found in the treated region. The other patients are free of tumor since two or three years. All patients tolerated the radiation very well. There were no problems in surgical techniques after the radiation. Especially in these advanced cases it is evident that only a combined theryp with exact timing can achieve good results.

OPTIMIZATION OF COMBINED RADIOTHERAPY AND SURGERY FOR ADVANCED PARANASAL SINUS CANCER

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2) University Radiology Center Freiburg i. Br., FRG
3) Radiological Clinic Münster, FRG

Combined radiotherapy and surgery is the treatment of choice as a rule in the majority of Centers in the last fifteen years. Radiation therapy is usually performed as a postoperative irradiation with telecobalt. The preoperative radiation therapy of paranasal sinus cancer is a debated question also at present.

The aims of our paper are, as follows:

1. The presentation of the result of combined radiotherapy and surgery of paranasal sinus cancer and the determination of the most effective treatment modality.
2. The presentation of our telecobalttherapy and intracavitary ^{60}Co brachytherapy optimization programme oriented to the type of tumor spread, suitable for combination with surgery.
3. The presentation of a combined radiotherapy and surgery treatment schedule, based on computer assisted radiotherapy optimization.

ad 1: 301 patients with paranasal sinus cancer were treated in this Institute[1] between 1946 - 1974. 157 patients were treated with combined radiotherapy and surgery, 133 patients undergone a solely radiotherapy. For the comparison of the treatment results achieved in the different patient groups, we investigated also the composition of the treated groups in the retrospective analysis and characterized it by the ratio of the number of patients with poor and good prognosis. The most favourable 42% 5-years-survival was obtained in patient group treated with preoperative irradiation + surgery + postoperative radiotherapy.

ad 2: The proved results obtained in malignant lymphomas with radiation therapy systematically oriented to the type of tumor spread have prompted application tumor spread oriented radiation therapy for tumors of other localizations.

Standardized radiation therapy techniques were used in the past for treatment of these malignancies, but the individual optimization assisted

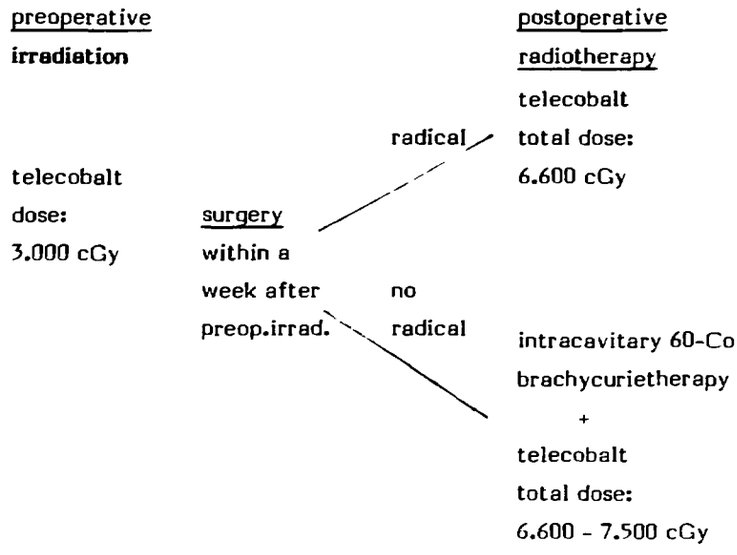
by CT based computerized treatment planning characterises the present external beam techniques. The question we tried to answer is: how far is possible to standardize and how far is necessary to individualize the radiation therapy of paranasal sinus cancer.

For approach by radiation therapy, four clinical situations should be considered, as follows: - advanced tumors with extensive bome destructions, - small tumors localized on the maxillary antrum (infrastructure), - tumors arising in, or secondarily involving the ethmoidal cells, and - residual tumors or recurrences.

Telecobalttherapy: Dose distribution of the irradiation techniques used for the treatment of paranasal sinus tumors was investigated in Alderson phantom by Philips TPS computer. By the systematic changing of the irradiation parameters it was attempted to develop field arrangements with optimal dose distribution and easy reproducibility and we tried to find quantitative optimization criteria for each of the four clinical situations. The computer calculations and TLD measurements were done simultaneously in two cross sections of the phantom, with regard to the different levels of the largest tumor extension, eyes and ethmoid cells. The field arrangements were tested on CT-cross-sections of paranasal sinus cancer patients. Optimization criteria and eye protection are discussed in detail.

Intracavitary Co-60 brachytherapy: Tumors of the paranasal sinuses are usually far advanced at the time of the first diagnosis. Response is often poor to dose applicable with external beam techniques. A high dose can be applied at a deep dose gradient with intracavitary technique and the dose delivery is protracted. Computerized treatment planning reduces errors in dosage. Considering the anatomy of the paranasal sinuses we constructed 11 different source arrangements, using 60-Co-spheres (diameter 7 mm, activity 5 - 10 mCi = 185 - 370 MBq), and calculated the isodose distribution of each at different levels in the frontal, sagittal and transversal plane with the brachytherapy programme of the TPS. This approach has made possible the stereoscopic reconstruction of the isodose distribution. A set of model source arrangements with calculated isodose distribution is available, which has made possible the selection of the most suitable scheme for a given clinical situation. Based on this set, the computerized treatment planning assisted 60-Co intracavitary brachytherapy method is described with well separable inactive and active phases. Indications for brachytherapy and radiation protection are discussed here. Investigations of the combined teletherapy and brachytherapy dose distribution showed, that the two techniques can be combined safely for treatment of paranasal sinus cancer.

ad 3: Based on these investigations, the following schedule should be the treatment of choice for paranasal sius cancer:



SURGERY FOLLWED BY HEMITHORAX-UPPER ABDOMEN IRRADIATION COMBINED WITH MULTIPLE-DRUG CHEMOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

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Eighteen patients with diffuse malignant mesothelioma were prospectively studied to assess the efficacy and complications of combined surgery, hemitherox-hemiupperabdomen irradiation and chemotherapy. Computerized axial tomography was used as a staging procedure, for assessment of treatment response and for evalutation of normal tissue damage. Effects on respiratory function were studied by spirometric indices from flow-volume curves and by diffusing capacity for carbon monoxide. Thoracotomy was performed in 17/18 patients, in 11 a subtotal surgical resection was attempted. Ten patients received a midline dose of 55 Gy/25 F/8 weeks, split-course, to the hemithorax from two opposed field covering the supraclavicular fossa, the entire thoracotomy scar, with 8 MeV photons. The areas with macroscopic tumor left received a boost of 15 Gy. The post-surgical tube orifices were irradiated separately; 55 Gy/22 F/5 weeks with 10 MeV electrons. Chemotherapy was given only to patients with stage III and IV tumors; 2 cycles CYVADIC before radiotherapy, 1 cycle during the split interval and 3 cycles following radiotherapy. Survival of 4/10 patients was 5, 8, 7 and 10 months after surgery and 6/10 are alive (1-12 months after surgery). Eight patients received only 20 Gy/10 F/2 weeks to the hemithorax followed by 3-16 cycles of chemotherapy. Median survival in this group was 18 months (range 6-48+). Severe, partly reversible radiation injury occurred after 55 Gy hemithorax-hemiupperabdomen irradiation. Our preliminary results suggest that aggressive multimodality treatment of malignant mesothelioma is ineffective in preventing local recurrence or blood-borne dissemination of the disease. Its benefit on quality of life was not objectively assessed.

INTRAOPERATIVE RADIOTHERAPY (IORT) PROJECT DEVELOPMENT

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Intraoperative radiotherapy (IORT), single high dose electron beam irradiation during surgical procedures, is currently being investigated as a new cancer treatment modality. This paper describes the development of an IORT project in The Netherlands and outlines organizational, clinical and physical aspects which must be considered in such a program.

INTRAOPERATIVE RADIOTHERAPY: THE NATIONAL CANCER INSTITUTE EXPERIENCE

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Intraoperative radiotherapy (IORT) is the delivery of single doses of radiation during surgical procedures, allowing shielding or displacement of normal tissues from the treatment volume and allowing direct irradiation of a tumor or resected tumor bed.

The National Cancer Institute (NCI) initiated studies of IORT in the late 1970's. Initial efforts were directed toward establishing safe dose guidelines for the clinical use of IORT. A series of experiments in dogs were carried out assessing the tissue tolerance to single doses of electron irradiation in normal and surgically-manipulated tissues, including abdominal viscera, pelvic viscera, and retroperitoneal organs. The radiobiology experiments showed that tissues tolerated IORT doses up to 3000 rad without significant complications. However, hollow viscera such as intestine or ureter showed progressive fibrosis and stenosis, with accasional occlusion or perforation at doses exceeding 3000 rad. On the basis of the NCI canine experiments, doses of 2000-3000 rad appeared to be within safe dose limits for the clinical application of IORT to human patients.

Eighty-five patients with various malignancies were treated at the NCI with surgery and IORT. All patients had advanced tumors which were considered to have little likelihood of cure by conventional therapy. Patients had surgical exposure of tumor, with gross resection of possible, combined with intraoperative irradiation. Some patients received additional postoperative external beam radiotherapy, and some received chemotherapy. The patient population treated included 32 with pancreatic carcinomas, 10 with gastric carcinomas, 20 with retroperitoneal sarcomas, seven with pelvic tumors, four with rectal tumors, and 12 with a variety of miscellaneous malignant neoplasms. Overall treatment results included an actuarial one-year survival of 71%, actuarial two-year survival of 58%, surgical mortality of 12%, and treatment complication rate of 25%. Local disease was controlled in 61% of patients, and 45% of patients remained clinically free of disease with a overall median follow-up of 22 months. The clinical experience suggested that it is feasible to combine IORT with extensive surgical procedures, that the morbidity of IORT with surgery is similar to the morbidity of operation alone in advanced malignant disease, and that IORT may promote the local control of advanced neoplasms.

TELE-ROENTGEN THERAPY IN VULVAL CANCER

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Radical vulvectomy and bilateral lymphadenetomy is considered to be the standard therapy of vulval cancer. The reported incidence of central recurrence in such treated patients varies from 18 - 34%. The operation in addition to carring the risks of major surgery esp. in aged patients, is a multilating procedure disturbing the body image and sexual function of the individual.

Roentgen therapy has been historically given a second place due to relatively poor tolerance of normal tissues of the region of interest to high tumoricidal doses.

The present study is the analysis 19 patients treated at Christian Medical College and Brown Memorial Hospital Ludhiana with surgery in various forms, radiation and the combination during last 7 years.

MATERIALS AND METHODS:

Nineteen prove patient of vulval cancer have been treated as follows:

(a) Radical vulvectomy ± bilateral lymphadenectomy - 7 patients,
(b) Simple vulvectomy + postoperative radiation to vulva and nodes - 7 and
(c) Radical radiotherapy only - 5 patients.

The results has been shown in table I - III.

In group (a) there was 1 death in postoperative period out 5 patients where radical vulvectomy and bilateral lymphadenectomy done at single patients while in other 2 planned for surgery in two phases, had come with massive nodal disease not responding to treatment.

The result of group (b) + (c) revealed good local response (10/12) both at moderate 40 - 50 Gy in 15 - 20 fractions over 3 to 4 weeks and radical doses 60 - 70 Gy in 30 - 35 fractions over 6 - 7 weeks used in split course fashion on propotionate expense of normal tissue damage though within permissible limits.

The response of the nodes was determinant to its size and amount of extracapsular infiltration.

COMMENTS:

(i) The aims of presentation of this study is to high light the advantages of this optimal combination of 2 local treatment modalites versus radical vulvectomy.

(ii) Owing to the relatively low incidence of this disease at one particular centre, it is to submit a plea for practising this combination for group trials as to evaluate its advantages out lined.

GROUP A

	No.of pts.	Follow up	Further Treatment
Radical Vulvectomy + Lymphadenctomy	5	4* NED	
Radical Vulvectomy	2	Fungating notes (8,10 months)	R.T. No response
	7		

*1 postoperative death

GROUP B

	No. of pts.	Follow up	
		Local recurrence	Distant
Simple Vulvectomy + Postop. R.T.	6	1* (3 months after treatment)	1
		1** (41 months after treatment)	
Recurrence after 5 yrs of Simple Vulvectomy	1	1 (45 months after treatment)	
	7		

* Subcut. spread ** Ca. in situ vulva & vagina

GROUP C

	No. of pts.	Follow up		
		Vulva	Nodes	Distant
Advanced disease + Bilateral nodes	2	+++ (18,20 months)	+++ (18,20 months)	-
Advanced disease + Fungating nodes	3	+++	+	Lungs 2 (Lymphangitis)
		++	+	
		+	+	
	5			

+++ - Good response ++ - Fair " + - Poor "

NEW PURPOSES OF PREOPERATIVE IRRADIATION FOR RECTAL CANCER

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High dose of external beam irradiation delivered in a short period of time is able not only to decrease the rate of local failures after surgery performed two months later but also to convert some tumors of the low rectum initially suitable for A.P. resection into lesions amenable either to restorative procedure or to conservative treatment. A series of 106 cases demonstrates the efficacy of the irradiation by Cobalt 60 sacral arctherapy 120° at a dose of 3000-3900 rad delivered in 12 days.

PREDICTIVE ASSAYS FOR THE THERAPY OF RECTUM CARCINOMA

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In order to improve the therapy of more resistant tumors individual biological data are necessary. Cytofluorometric DNA measurements showed that about 60 percent of rectum carcinoma (81 patients) had hyperploid tumor cell lines. For patients with such a tumor the prognosis was worse than for patients with diploid tumors. From the DNA histograms the number of S-phase cells was calculated. In those T_3 tumors (clinical staging), which disseminated to lymph nodes or metastasized, a higher number of S-phase cells was found than in tumors with the staging $T_3N_0M_0$.

In all untreated tumors cells with micronuclei were found. This observation demonstrates cell loss. In most tumors this was considerable. The ratio: number of S-phase/number of cells with micronuclei gives a rough estimate for cell turnover in the tumor. In patients with a bad prognosis and a local recurrence after surgical resection of the tumor this ratio was high.

In some patients the parameters were measured before and after preoperative radiotherapy. In some tumors a rapid increase of S-phase cells occurred after irradiation. In these patients local recurrences were found. From the determination of SH-groups which are bound to proteins in the cell nucleus also a prediction for local recurrences could be made. The determination of micronuclei indicated the radiation response in the tumors.

All parameters showed a high variability between individual tumors and may be used for the prognosis of the disease. However, it has turned out that one assay is not sufficient in order to obtain predictive data but that the combination of several assays can give a prognostic figure.

RADIOTHERAPY

AND

HYPERTHERMIA

Saturday, March 30, 1985

MOLECULAR RESPONSE TO HYPERTHERMIA
CLINICAL IMPLICATIONS

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For approximately a decade hyperthermia has been examined as an experimental procedure in treating cancer. However, in addition to it's capacity to result in cell death, a cell's response to heat also encompasses several more interesting aspects of cell behavior. We summariz· here our previous studies on this topic and suggest some possible applications. This is not intended as an overview of the field, but as a summary of the work performed in the Department of Radiation Medicine at Roswell Park. In this same meeting in 1981 we suggested a role for heat shock proteins (hsps) in the phenomenon thermotolerance. Our subsequent studies have largely supported the impression that a connection between these phenomena exists, however a causative role for hsps in thermotolerance is still not established. To learn more regarding this possible connection and to further unterstand how these proteins might function we became interested in determining their cellular local. We, therefore, prepared an antisera against the 110kDa hsp and demonstrated that this hsp is a nuclear protein with a particularly strong affinity for nucleoli. In addition to hsps we also recognized that other inducible protein systems were present and set about the investigation of these systems. The glucose regulated protein system induced in the absence of glucose is one of these systems. We induced these glucose regulated proteins (grps) and examined their ability to confer thermotolerance in analogy to our earlier heat shock protein work. To our surprise, not only were the grps unable to confer thermotolerance, they were found to correlate with a two log thermosensitization. We also observed that when glucose was restored to the media of such sensitized and grp induced cells, the repression of the grps was accompanied by the induction of the hsps. A small degree of thermotolerance resulted.We have also demonstrated that the anaerobic shock proteins induced under anoxia (and in the presence of glucose) are identical to the grps and that restoration of oxygen to cells again induces the hsps, in a manner somewhat analogous to glucose deprivation and release. While the molecular basis for thermotolerance is still a mystery, it now appears to be related in some way to the funcion or purpose of the hsps. The nuclear/nucleolar localization of at least one major hsp suggests a role at transcriptional or post-transcriptional levels. However the relationsship between this and tolerance remains an important question. The possible connection between glucose and oxygen deprivation and grps and release from these states and the induction of hsps presents an additional set of constraints for the expression and control of these two

different stress protein systems. Nutrient (i.e., glucose) and/or oxygen deprivation are likely occurances in some tumors. Thus, the possible induction of grps in deprived regions of tumors is a possibility and phenomena such as reoxygenation (during radiotherapy) may alternately induce hsps. The in-vitro connections relating the expression of both stress protein systems with significant changes in resistance or sensitization to hyperthermia indicates that these phenomena may significantly alter the tumor's response to this type of cancer therapy.

A METHOD OF ASSESSING THERMAL DOSE

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As yet there is no satisfactory method of defining "thermal dose". However, in order to relate different hyperthermal treatment, the relationship between heating time and temperature is often used to derive an "equivalent heat treatment" (Field and Morris, 1983, Sapareto and Dewey, 1984). The following relationship

$$\frac{t_2}{t_1} = R^{T_1 - T_2}$$

where t = treatment time
T = temperature
R = 2 for T ≥ 42.5
R = 4-8 for T ≤ 42.5

has been derived from many in vivo and in vitro studies which relate time and temperature to produce a given level of injury in a single treatment.

Using an animal model system, i.e. the response of the baby rat tail, the validity of the above equation has been tested in a variety of conditions aimed at simulating a clinical treatment. Initially it was shown that the phenomena of thermotolerance and step-down heating could clearly be demonstrated. Tails were then alternated between water baths at different temperatures using a variety of conditions, to simulate the effect of a varying temperature. The measured effects were compared to a prediction based on the above formula. In general the agreement was satisfactory, the maximum difference between the observed and predicted effect, obtained under exreme conditions unlikely to be experienced clinically, amounted to an underestimate of the effective temperature by 0.3°C.

The value of such an equivalent heat dose on the development of clinical hyperthermia will be briefly discussed.

COMBINED EFFECT OF DIETHYLDITHIOCARBAMATE (DDC) AND HYPERTHERMIA (41°C) ON CHINESE HAMSTER (V79) CELL SURVIVAL AND DNA STRAND BREAK REPAIR FOLLOWING IRRADIATION

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When Chinese hamster V79 cells in culture were irradiated with single doses up to 1000 rad of gamma rays from cesium 137, pre-incubation with 10^{-4}M DDC had no effect on cell survival at 37°C but markedly decreased survival at 41°. The mechanism of this increased cell killing by pre-incubation with DDC at 41° is not known. However, when the cells were incubated with 10^{-4}M DDC before and after irradiation, repair of DNA single strand breaks proceeded normally at 37° but could not be observed at 41°. The implication of these findings will be discussed.

Paper will not be presented

IN VIVO INVESTIGATIONS OF LOCAL TEMPERATURE CHANGE IN TISSUE AND FIRST CLINICAL EXPERIENCES USING ULTRARED A

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University Clinic for Radiotherapy and Radiobiology, Vienna, Austria

To obtain objectivity of the temperature increase we first investigated this method on pigs in vivo (more than 150 measuring points). Later 30 patients suffering from skin metastasis were treated by this method.

In the below mentioned investigations and treatments we employed an ultrared A device WMS 500. The wave length of ultrared A is defined from 800-1200 nm.

The pigs were narcotized and heated on the musculus gluteus max. Before heating the temperature was measured as deep as 5 cm at specified points. Immedeately after ending the heat treatment we measured the temperature change analog to the previous reference measurements. At a depth of 5 cm we could measure only a very small temperature increase of about 1 to 2° C.

Similar investigations on unnarcotized human patients showed comparable results. In accordance to our previous investigations no temperature change was measured intrauterine either before, during or after a gynaegological heat treatment.

Based on our measurements we combined ultrared A and electron radiation treatment only for superficially located tumors especially for skin metastasis of mammary carcinoma. The obtain objective results of our combined treatment technic, only half of the electron treated area was warmed up by ultrared A. The area of combined treatment showed earlier respondence as the only electron irradiated region.

THE COMBINED TREATMENT OF TUMORS BY HYPERTHERMIA AND HYPERGLYCEMIA AFTER IRRADIATION IN AIR OR TOTAL-BODY HYPOXIA

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It has been shown recently that the survival of irradiated Ehrlich carcinoma cells conciederably decreases if they are incubated with glucose in anoxic conditions in vitro or if short-therm (2-2,5 hours)hyperglycemia is induced in organism immediately after irradiation (10-30 Gy) of solid tumours. This phenomenon is concidered as a result of the intensive interphase death of tumours cells which in turn is the result of interaction of the followeing interrelated factors: the impairment of microcirculation, the diminuition of pH level, suppression of lactate removal and, which is especially important - the action of anoxia (or severe hypoxia). At the same degree of pH, but under normal oxygenation, the radiomodifying effect of glucose disappears or drastically decreases. The molecular mechanism of the phenomenon discovered is considered to consist in the development of postulated potential damages in cell membranes.

These data permitted to develop an effective scheme of utilization of hyperglycemia and hyperthermia after irradiation of tumors in animals breathing air or hypoxic (6% O_2) gas mixture. Immediately after local irradiation mice receive 5 i.p. injections of 40% glucose solutions - 3 times by 2,6 g/kg and 2 times - 1,3 g/kg with 30 min interval. After this procedure the glucose concentration in serum elevates up to 2o - 25 mM. 3o min after last administration of glucose the tumors, transplanted into the thigh, are heated in the water bath 30 min of 43° C according to the method of Overgaard.

The combined treatment of mice by this method which we call polyradiomodification increases the fraction of controlled (120 days) tumors up to 4 times in comparison with the individual application of these modifying agants. The control of tumour grouth is achieved in 80 - 90% of mice with 30 Gy irradiation with simultaneous twicely diminution of skin reactions. Polyradiomodification was effective also at the smaller level of the dose of irradiation, permitting tumour eradication in 60 and 30% of animals after 20 or 10 Gy.

Due to the favorable selectivity of action of these agents on tumors and skin the therapeutic gain factor reaches 5, which seems to be rather high value. This method now is under clinical investigation.

THE EFFECT OF PREHEAT TREATMENT ON THE SENSITIVITY OF EMT6 CELLS TO ADRIAMYCIN

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We have previously investigated the cytotoxic effect of the interaction between hyperthermia and adriamycin on EMT6 cells in vitro (Morgan et al, Br.J.Cancer 79, 422, 1979). Data presented confirmed the heat enhancement of cytotoxicity first reported by Hahn & Strande (J.Natl.Cancer Inst. 57, 1063, 1976) and also demonstrated the protective effect of thermal tolerance induced by a period of preheat for 1 hour at 43°C before the subsequent heat (at 44°C) with adriamycin.

Hahn &Strande (1976) demonstrated increased uptake of adriamycin in heated cells and ascribed the increased toxicity to this effect. Their uptake experiments were carried out at an adriamycin concentration of 30 ug/ml which is 10x higher than that used to assess the cytotoxicity.

We have investigated the uptake of adriamycin using flow cytometry at drug concentrations at which cytotoxicity may also be assessed (0 - 10 ug/ml). Uptake of adriamycin by cells at 37°C is reduced after preheating in the absence of drug for 1 h at 43°C. This effect is abrogated by permeabilising the cell membrane by freeze thawing.

Correlation of the intracellular adriamycin concentration with summary fraction after cell kill shows a greater sensitivity of preheated cells to a given intracellular concentration of adriamycin than for unheated ones. We conclude, therefore, that pre-heated cells accumulate less adriamycin in their centres, as has been previously reported, but also that the preheated cells are less sensitive to the drug that passes through the cell membrane.

HYPERTHERMIA-RESULTS OF 270 TREATED PATIENTS

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Between 1979 and 1983 270 patients were treated with a combination of radiotherapy and hyperthermia by capacitive heating (13,56 MHz). The results of 246 patients with advanced solid tumors were evaluable. Overall 33% complete remissions and 32% partial remissions were observed. In 19% of these cases no change was seen and 8% of the patients were non responder or showed tumor progression. The best remission rate had the group with breast cancer 8/15 (80%) with recurrences 34/44 (73,3%) and with head and neck tumors 48/67 (71,6%). The poorest results were seen among the glioblastoma and the lung cancers. The combined treatment was well tolerated and there were only few patients who had local problems. 3 of them had ulcerations of the skin caused from poorly placed electrodes.

CONFORMATION RADIOTHERAPY COMBINED WITH LOCAL HYPERTHERMIA BY 8 MHZ RF-WAVE FOR DEEP-SEATED MALIGNATNT TUMORS

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In order to investigate the combined effect between irradiation and hyperthermia for the deep-seated malignant tumors, the RF capacitive heating at 8 MHz was applied. Thermal measurements have been performed on the phantoms having electrical characteristics of human soft tissues. Different size applicators were used according to the location and size of the lesion, so that a high temperature area could coincide with the malignant lesion.

Clinically, the focusing effect may be modified by thermal dissipation due to blood flow and heterogeneity of the human body. In order to abtain good results in utilizing radiopotentiation of hyperthermia, it is important to irradiate the tumor homogenously, and at the same time, to protect the surrounding healthy tissues as much as possible. From this standpoint, the conformation radiotherapy was used together with the combination of the local hyperthermia. The conformation technique is an improved type of rotation therapy reported by Prof. Takahashi in 1960.

Since January in 1982, the clinical investigation is carried out in the patients with the deep-seated malignant tumors, especially hepatoma and carcinoma of the uterine cervix. Local hyperthermia was administered twice a week, 60-120 minutes after radiotherapy.

The technical problems arising in these combined treatments and the clinical/pathological results will be discussed.

Nia 15 mg

NOVO

MEGESTROLACETAT
für die Hormontherapie
des Endometrium-
karzinoms

Megestrolacetat ist als
Progesteronabkommling
ein REINES GESTAGEN

Die klinischen Erfahrungsberichte heben hervor.

- Das objektive Abklingen von Rezidiven und Metastasen in 30–40% der Fälle
- Die subjektive Besserung, auch bei Patienten im fortgeschrittenen Stadium
- Die seltenen und unwesentlichen Nebenwirkungen

Zusammensetzung
Jede Tablette enthalt 15 mg Megestrolacetat (6-Methyl-6-dehydro-17α-acetoxyprogesteron)
Indikationen
Rezidive, Metastasen und inoperable Falle von Endometrium-Karzinom
Dosierung
Anfangsdosis 2x taglich 2 Tabletten entsprechend einer Tagesdosis von 60 mg Wenn innerhalb von 3–6 Wochen ein positiver, aber nicht ausreichender Einfluß gesehen wird, ist Dosiserhohung auf 2x taglich 5 Tabletten (150 mg Tagesdosis) angezeigt
Diese Therapie wird ohne Unterbrechung weitergefuhrt Eine Reduktion der Dosierung soll erst dann erfolgen, wenn die totale Regression seit mindestens 2 Jahren konstant war In diesem Fall kann auf 1–2 Tabl Nia 15 pro Tag gesenkt werden Mit dieser Dosis wird auf unbestimmte Zeit fortgesetzt
Nebenerscheinungen
Toxische Wirkungen wurden nicht beobachtet Vereinzelt wurde uber Erbrechen berichtet
Kontraindikationen
Schwangerschaft Andere Indikationen fur Gestagene
Handelsform
Nia 15 mg, Packungen zu 120 Tabletten

Edgren R A et al
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