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A NEW CLASS OF DRUG ABLE TO MODIFY THE IMPACT OF LOW LET RADIOTHERAPY.

Gramaglia A., Morazzoni F., Villa S., Leonardi M.C., Razzini E., Milani F., Palazzi M., and Baronzio GF.
National Cancer Institute, Milan - Italy.

The main problem in low LET RT is to achieve a strict relationship between radiation dose-distribution and biological effect. Some neglected parameters could be modified by a new class of drug, omega three fatty acids (W-3), to yield a more homogeneous effect-distribution within the irradiated media: tumor blood rheology, tumor interstitial fluid formation and pressure, and tumor lipoperoxidation. All these parameters play a relevant role on modifying the oxygen enhancement ratio (OER), that is the main radiobiological tool of low LET RT, working at three different stages: oxygen supply, oxygen transport and cooperation between normal peroxidation chains and H202 produced by RT. Rationale, methods of measurement and results (regarding mainly to blood rheology) will be discussed in detail.

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Saran F., Zamboglou N., Akerboom TPM., Adamietz IA., Mose S., Schmitt G., Böttcher HD., Dept. of Radiotherapy
Johann Wolfgang Goethe-University, 6000 Frankfurt a.M. 70, Germany

CHANGES OF FREE INTRATUMORAL GLUTATHIONE LEVELS AS BIOLOGICAL PARAMETER IN PATIENTS WITH ADVANCED HEAD AND NECK TUMORS

The tripeptide glutathione (GSH), glutamylcysteinglycine, the major free thiol in most living cells, is due to his redoxsystem with glutathione disulfide (GSSG) a wellknown intracellular radical protector. After irridiation it is an important factor of radioprotection and influences radioresistance. There is no reliable information over GSH levels in tumors in vivo, the GSH changes under radiation and its correlation with clinical outcome.

Biopsies of 10 patients with advanced head and neck cancers (T3-T4, N0-N3, M0) were taken before and immediately after 2 Gy. After homogenisation and treatment with 7% perchloric acid, glutathione was linked with a dithiobisnitrobenzoic acid (CDNB) and spectophotometrically followed at 340/400 nm (Sigma ZWS II). The proteine was measured according the method of Lowry. Median follow up was 36 months. The pretherapeutical glutathione levels showed a great individual variance ranging from 0.39 to 3.86 µmol /g wet weight (average: 1.56 ± 1.27 µmol/g ww). Immediately after the first radiotherapy of 2 Gy the glutathione levels decreased in average for 51.3% to 0.80 ± 0,61 µmol/g ww. Patients with pretherapeutical glutathione levels ¼ 0,68 µmol/g ww showed a significantly longer disease free and overall survival (log rank test, p<0.001).

The redoxmechanism between oxidated and reduced glutathione as well as the pretherapeutical glutathione level may play an important role in intrinsic radioresistance of advanced head and neck cancers and can probably serve as prognostical biological parameter.

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INITIAL DNA DAMAGE DOUBLE STRAND BREAKS CELLULAR RADIOSENSITIVITY

Ruiz de Almodóvar JM, Núñez MI, McMillan TJ, Olea N, Mort C, Villalobos M, Pedraza V, Steel GG.

Department of Radiation Oncology. Tumor Biology Laboratory. University Hospital. School of Medicine. Granada. Spain. The Institute of Cancer Research. RRU. Sutton, Surrey. UK

In the present work we report the results of our study designed to elucidate the role of the initial DNA damage (induction of double-strand breaks, dsb) as a determinant of cellular radiosensitivity. Four human breast carcinoma cell lines (MCF-7 BB, MCF-7 BUS, T47D-81 and T47D-BB) and one human bladder cancer cell line (RT-112) were used. Cell survival was measured by monolayer colony-forming assay as appropriate and a large variation in sensitivity was seen (α-values of 0.120 to 0.536). As expected we found a significant relation between α and the surviving fraction at 2 Gy (SF2). The dose-response curves for DNA retained in the wells were biphasic with a flattening of the curves above 30 Gy. Data corresponding to the initial slopes of PFGE dose-response curves showed no relationship with α and SF2 values. However, when the frequency of DNA dsb induction was assessed using a mathematical model based on the DNA fragment size distribution into the gel lane, we found a statistically significant relationship between the number of DNA dsb induced and the corresponding α and SF2 values ($p = 0.0054$ and $p = 0.0110$, respectively). These results support the view that sensitive cells suffered a larger number of lesions per Gy than resistant cells.

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ARE α/β RATIOS DERIVED FROM HYPOXIC TUMORS TOO HIGH?

R. Guttenberger

Department of Radiotherapy,
Albert-Ludwigs-Universität, Freiburg,
Germany

Hyperfractionation may spare tumors more than previously believed. This is because one aspect involved in deriving α/β values has not been duly considered, i.e. hypoxia.

The problem arises even when α/β values obtained from clamped tumors are converted into values for euoxic tumor cells, - if this is done by dividing by an average OER (oxygen enhancement ratio).

A different approach was adopted assuming that the OER varies between 2.4 and 2.8 in a dose-dependant way [Palcic & Skarsgard, 1984, Radiat.Res.100:328-339]. In order to envisage the significance of this effect, published data was reanalyzed.

In conclusion, α/β values derived by division by an average OER are far too high, if the OER increases with dose. A more accurate way to obtain oxic α/β ratios is to convert the doses given under clamp hypoxia into oxic doses by division through the dose-dependant OER before estimating the α/β ratio.

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STUDIES ON c-Ha-RAS AND c-MOS ONCOGENE REARRANGEMENTS IN HUMAN UTERINE CERVIX CARCINOMAS DIFFERING IN RADIOSENSITIVITY

Polischuk A[1], Lewensohn R[1] and Zhivotovsky B[2]

[1]Dept of Oncology, Radiumhemmet and [2]Dept of Toxicology, Karolinska Institute, S-104 01 Stockholm, Sweden.

Cancer of uterine cervix is the most important female malignancy which is treated by radiotherapy. An association between oncogene expression and radiosensitivity of tumour cells has been suggested. In particular a correlation between activated forms of c-Ha-RAS, presence of c-MOS oncogenes and cellular radioresistance has been shown.

The present study focuses on the relation between these oncogenes and radioresistance in clinical biopsies from human carcinomas of the uterine cervix. For the analyses of the structure of c-Ha-RAS and c-MOS the method of southern-blot hybridization was used. DNA obtained from 65 pts mainly stage II and III were examined. Rearrangements of the c-Ha-RAS oncogene were found in 14 biopsies, whereas rearrangements of the c-MOS oncogene were observed in 9 biopsies. Data involved will be discussed in relation to the clinical radiosensitivity of the tumours.

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FROM STRANDQUIST TO L-Q FORMULA-
IS HUMAN SKIN CANCER A GOOD MODEL
FOR RADIOBIOLOGY

B.Maciejewski*, A.Hliniak**
Centre of Oncology, M.Skłodowska-Curie
Memorial Institute, Gliwice*, Warsaw**,
POLAND

The data of 946 skin cancer patients treated with single doses or with 4,8,17,40 or 47 fractions of X-rays were analyzed to check the validity of Strandquist, NSD and L-Q models. Strong correlation between size, control rate and dose fractionation was found. For small tumors, single dose was as effective as fractionated treatment, for large tumors high local control can be obtained after 70 Gy in 47 fractions. The data indicate a non-linear dose-time relationship and a steep increase in TCD_{50} vs time reflecting accelerated repopulation of tumor clonogenic cells (1.0 Gy/day beyond day 55 of treatment time). With L-Q model, an α/β value of 13.0 Gy for tumor was calculated and cell survival curves were constructed. From these curves the D_0 values of 0.88 - 2.0 Gy were calculated. The number of clonogenic cells of less than one in 10^8 tumor cells was estimated and no influence of hypoxic cells on local tumor control could be demonstrated.