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The prognostic value of serum osteopontin, HIF-1alpha and pO2 measurements in advanced head and neck tumors treated by radiotherapy.

M. Nordsmark, J. Alsner, J.G. Eriksen, M.R. Horsman, J. Overgaard. *Dept Experimental Clinical Oncology, Oncology, Aarhus, Denmark*

Background: Several studies have shown that tumor hypoxia adversely influences prognosis after radiation therapy. But there is a need for clinically useful hypoxia specific prognostic assays. The aim of this study was to compare osteopontin (OPN) shown to be expressed in hypoxic cells with hypoxia inducible factor 1α (HIF-1α) and measurement of physiological tumor oxygenation and to evaluate the prognostic value of these assays in advanced head and neck cancer.

Methods: The study included a total of 55 patients with primary head and neck cancer that all received primary radiation therapy. Serum samples were analysed for OPN using an Elisa assay, histological sections were subjected to immunohistochemical analysis for HIF-1αand tumor oxygenation measurements were made with the Eppendorf oxygen electrode. Endpoints were loco-regional tumor control (LC) and disease specific survival (DSS) at 5 years.

Results: There was large inter patient variability in all 3 measures of hypoxia. Serum OPN had a median of 628 ng/ml (range 168-3790). Absence of HIF-1αstaining was found in one third of patients, between 0-50% HIF-1αstaining in another third and >50% HIF-1αin the final third. Measurements of tumour oxygenation showed a median pO_2 of 10 mmHg (range 0-54) and percentage of values ≤ 2.5 mmHg ($HP_{2.5}$) a median of 28% (range 0-95). The correlation between OPN and median tumour pO_2 was statistically significant (p=0.03) whereas OPN and HIF-1α did not correlate (p=0.14). In survival analysis, when grouping patients into 3 of either OPN, HIF-1α or $HP_{2.5}$, patients with the highest levels of OPN and $HP_{2.5}$ had significantly poorer LC probabilities (p=0.01 and p=0.001, respectively) while patients with HIF-1αscores >50% also did poorly in LC though not statistically significant (p= 0.22). Using DSS as the endpoint, patients with high OPN or HIF-1α labelling above 50% had a statistically significant poorer prognosis (p=0.009 and p=0.05, respectively) while there was a trend that patients with high $HP_{2.5}$ did worse (p≈ 0.06).

Conclusions: OPN correlated with pO_2 but not HIF-1α. Patients with low tumor pO_2 had poorer LC at five year whereas high HIF-1α labelling had a negative effect on DSS. However, OPN was prognostic for both LC and DSS.

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Quality assurance report of EORTC 26981/22981 trial on radiotherapy vs radiotherapy and temozolomide for newly diagnosed glioblastoma multiforme: individual case review

F. Ataman[1], P. Poortmans[2], R. Stupp[3], R.O. Mirimanoff[3]. [1] *EORTC, Radiotherapy Group, Brussels, Belgium and Akdeniz University, School of Medicine, Department of Radiation Oncology, Antalya, Turkey;* [2] *Dr. Bernard Verbeeten Instituut, Radiation Oncology, Tilburg, The Netherlands;* [3] *Centre Hospitalier universitaire Vaudois, Medical Oncology, Lausanne, Switzerland;* [4] *Centre Hospitalier universitaire Vaudois, Radiation Oncology, L ausanne, Switzerland*

For the EORTC Radiotherapy and Brain Group Purpose: To assess the compliance to protocol guidelines, where conventionally fractionated focal irradiation is used. The analysis focused on dose-volume evaluation and radiotherapy procedures.

Methods: All participating centres (84) were asked to send data on a randomly selected patient. The required data included surgery, pathology and radiology reports, relevant imaging, simulation films, treatment charts, plans and portal films along with a completed short technology questionnaire. Parameters, related to radiotherapy preparation and execution were analyzed.

Results: Up to now, 35 (41%) centres responded. All of the patients are eligible without any discrepancies between actual and reported data on type of surgery and tumour localization. All centres use immobilization devices and 2D or 3D CT based treatment planning. Field shaping is done by customized blocks (24) or MLC (11). All centres use appropriate photon energy (≥ 4 MV). Treatment verification is done by only portal films (27), only EPID (2), portal films &EPID (2) and portal films & TLD (4). The frequency of portal imaging was at least once (20), weekly (11) or unknown (4). The majority of centres delineate PTV and organs at risk. All centres produce dose distribution plots and 29 centres compute DVH. All patients received 60 Gy in 30 fractions as stated in the protocol except for 2, where a field reduction was necessary to comply with the dose-volume constraints of the protocol. Overall treatment time was ≤ 6 weeks in the vast majority (33). All centres specify the dose to the isocenter of the beams. The maximum and minimum doses within the PTV are reported in 28 (80%) centres. Dose homogeneity is according to ICRU 50 for 18 (50%) centres. PTV coverage is ≥95% for 13, 95% for 5 and 90% for 10 patients, respectively. The under-dose is limited to a very small part of the PTV for all cases. The maximal dose to the optic chiasm and brain stem is below the tolerance level in the majority of patients. For 4 cases, the maximal dose exceed slightly tolerance dose and it was unknown in 5.

Conclusion: All responding centres have the technical capabilities to deliver radiation according to the protocol guidelines. The performance of dose planning is at least level 2 according to ICRU 50 in the majority of centres. Overall, the compliance to the protocol requirements is very good to excellent.

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GENEPI - the European normal and tumor tissue bank and database: a new ESTRO activity

T. Hoelscher[1], Ch. Verfaillie[2], M. Baumann[1,3]. [1] *Dep. of Radiation Oncology, Medical Faculty of the TU Dresden, Dresden, Germany;* [2] *ESTRO of fice, Brussels, Belgium;* [3] *on behalf of the GENEPI project group*

Background: Recent progress in molecular and cell biology shows strong evidence for a genetic basis for radiation responses in normal tissues as well as in tumours. To create an infrastructure for molecular research in irradiated patients, the ESTRO-GENEPI project was initiated. The aim of GENEPI is to create a European tissue bank linked to a detailed outcome-database of a large cohort of patients receiving radiotherapy.

Material & Methods: The structure of the GENEPI project will be presented in detail.

Results: A normal and tumour tissue bank from irradiated patients with H&N, breast, rectal or prostate cancer will be linked to a detailed clinical outcome database. A central database will be established to provide a link to existing decentral databases and tissue banks. This will foster optimal utilisation and access to data and material. Protocols for outcome assessment, tissue handling, and use and access of the infrastructure will be developed. Furthermore, protocols for inclusion of patients by European centers into this project will be set. Ethical and legal aspects within the European context will be evaluated. It is planned to store lymphocytes, skin, mucosa and tumour tissue of cancer patients for at least 20 years and keep it available for future large scale research projects.

Conclusion: The GENEPI project of ESTRO will generate a clinical, biological and biostatistical network that is expected to become an important resource for biomedical research in the field of radiation biology and effects of radiation therapy.

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Biological assessment of mixed beam irradiation of carbon-ion and X-ray

Y. Demizu[1], K. Kagawa[2], Y. Ejima[1], H. Nishimura[1], R. Sasaki[1], T. Soejima[1], K. Sugimura[1], Y. Hishikawa[2], Y. Furusawa[3]. [1] *Kobe University Graduate School of Medicine, Radiology, Kobe, Japan;* [2] *Hyogo Ion Beam Medical Center, Radiology, Ibo-gun, Japan;* [3] *National Institute of Radiological Sciences, Laboratory of Heavy-ion Radiobiology for Therapy, Chiba, Japan*

Background: Carbon-ion beam therapy is a promising technology because of its superb biological effects, even for radioresistant tumors, and excellent dose distribution. However, serious adverse effects have also been reported due to the difficulty of avoiding irradiating normal tissues. Moreover, it is an expensive technology, and requires a lot of human resources and time. Mixed beam irradiation with X-ray may provide an answer to these problems. Therefore we researched the biologic effects of mixed beam irradiation of carbon-ion and X-ray at Hyogo Ion Beam Medical Center to assess its possible clinical applications.

Material and Methods: Cultured cells from human salivary gland cancer (HSG cells) were used for all experiments. The following conditioned cells were prepared: cultured under standard condition (Normal), cultured under hypoxic condition for 24 hours before irradiation (Hypoxia), and synchronized in late S-phase of cell cycle by serum starvation technique (Synchronized); Hypoxia and Synchronized are both radioresistant conditions. Cells were irradiated with 320 MeV carbon-ion only (CC), 4 MV X-ray only (XX), or