680 PUBLICATION

The reconstruction of the lacrimal ducts in the cancer of the eyelids and the medial angle of the eye

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Purpose: Skin cancer located in the region of the medial angle of the eye, on the medial part of the upper and lower eyelids infiltrates and eventually closes the lacrimal ducts, which causes the leaking of tears onto the cheek.

Methods: In the years of 1997–99, in five patients, apart from the reconstruction of the eyelids, the outflow of tears was made by drilling a hole in the lacrimal bone through which a drain (/ 3 mm) was introduced to connect the conjunctival sac with the nasal dactule. The drain was removed after ten days.

Results: The ambulatory examination showed good cosmetic effects, and confirmed that tears flow out through the natural way to the nasal dactule. These results were also confirmed by the contrast examination.

Conclusion: Connecting the conjunctival sac with the nasal dactule by drilling a hole in the lacrimal bone is a good way of construction of the outflow for tears in the advanced cases of carcinoma of the eyelids and skin of the medial angle of the eye.

Radiobiology

681a ORAL

Abstract not received.

681b ORAL

Abstract not received.

682 ORAL

Alkyl-lysophospholipids activate the SAPK/JNK signaling pathway and enhance radiation-induced apoptosis

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Alkyl-lysophospholipids (ALPs) represent a new class of anti-tumor drugs that induce apoptosis in a variety of tumor cell lines. Although their precise mechanism of action is unknown, ALPs primarily target the cell membrane where they inhibit signaling through the mitogen-activated protein kinase (MAPK) pathway. Since stimulation of the stress-activated protein kinase (or c-Jun N-terminal kinase; SAPK/JNK) pathway is essential for radiation-induced apoptosis in certain cell types, we tested the effect of ALPs in combination with radiation on MAPK/SAPK signaling and apoptosis induction. We present data showing that three clinically relevant ALPs (Et-18-OCH3, HePC and the novel compound D-21266; ASTA Medica AG) induce time- and dose-dependent apoptosis in the human leukemia cell lines U937 and Jurkat T ($ED_{50} \sim 8\ \mu M$). Moreover, in combination with radiation, ALPs strongly enhance the induction of apoptosis, reaching levels of 80% after 16 h. All tested ALPs not only prevented MAPK activation, but, like radiation, stimulated the SAPK/JNK cascade 5–10 fold within minutes. A dominant-negative mutant of c-Jun inhibited radiation- and ALP-induced apoptosis, indicating a requirement for the SAPK/JNK pathway. Our data support the view that ALPs and radiation cause an enhanced apoptotic effect by modulating the balance between the mitogenic, anti-apoptotic MAPK and the pro-apoptotic SAPK/JNK pathway.

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Improving anti-cancer therapy by targeting the tumour vasculature with combretastatins

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Purpose: Combretastatins are a new class of tublin binding agents that appear to have anti-tumour activity by specifically damaging the tumour vasculature. The aim of this study was to investigate the potential of the lead compound, combretastatin A-4 disodium phosphate (CA4DP), to improve the effect of conventional anti-cancer therapies.

Methods: A C3H mammary carcinoma grown in the right rear foot of female CDF1 mice was used when tumours had reached to 200 mm^3 in size. We combined single radiation or hyperthermia treatments with CA4DP. Radiation response was determined by the TCD50 dose (radiation dose producing local tumour control in 50% of treated animals) 90 days after treatment. Thermal response was estimated by the tumour growth time (TGT; time taken for tumours to grow to 5× treatment volume) after heating at 42.5°C for 60 minutes

Results: The TCD50 dose (95% confidence interval) for control tumours was 52 Gy (50–55) and this was significantly decreased ($p < 0.05$) to 46 Gy (42–49) if mice were i.p. injected with 250 mg/kg CA4DP 30 minutes after irradiation, but only to 50 Gy (46–54) with 100 mg/kg CA4DP. The mean (±S.E) TGTs for tumours given either no treatment, 250 mg/kg CA4DP, or heat alone were 6.6 days (±0.5), 8.0 days (±0.6) and 12.8 days (±0.8), respectively. Injecting 250 mg/kg CA4DP 30 minutes prior to heating significantly increased the TGT to 15.6 days (±0.6). This thermal enhancement was independent of the drug dose from 25 to 400 mg/kg.

Conclusion: Radiation and hyperthermia therapy can be enhanced by combretastatins, but the drug-dose dependencies are different.

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Intratumoral microvessel density predicts local failure of radically irradiated squamous cell cancer of the oropharynx

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Purpose: To determine the predictive value of the intratumoral microvessel density (IMD) and expression of vascular endothelial growth factor (VEGF) for the radiocurability of pts. with squamous cell cancer of the oropharynx.

Methods: From 10/91 until 12/98 116 pts. with squamous cell cancer of the oropharynx were radically irradiated in our department. 151 paraffin embedded biopsies were analysed by immunohistochemistry (anti-CD31 for IMD, anti-VEGF). IMD was determined in hot spot areas at 200× magnification. VEGF expression was semiquantitatively determined (0, +, ++, +++).

Results: Increasing IMD (range 54–282) was strongly correlated with local failure as shown by multivariate Cox regression analysis (IMD as continous variable; $p = 0.0002$), whereas VEGF expression (0/+ vs. ++/+++; $p = 0.3347$) was not. When the IMD was categorized into 4 groups, the risk ratio for local failure increased from 2.71 (80–110) to 4.55 (111–130) and 13.01 (>130) compared to the base line group (<80). Moreover, pts. with PR or progression during radiotherapy had a significantly higher mean IMD than pts. with relapse after CR or pts. with continous CR (127.2 vs. 110.8 vs. 100.0; $p = 0.02$). There was no correlation between IMD and VEGF expression (Wilcoxon rank sum).

Conclusions: IMD is a strong predictive factor for treatment failure in radically irradiated squamous cell cancer of the oropharynx.

685 ORAL

Magnetic resonance perfusion imaging correlates with tumour oxygenation but not angiogenesis in carcinoma of the cervix

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Purpose: To compare the relationship between magnetic resonance (MR) perfusion imaging parameters, tumour oxygenation and vascularity in carcinoma of the cervix.

Methods: Gadolinium enhanced MR imaging was performed in 15 patients with stage Ib–IIIb carcinoma of the cervix prior to treatment and repeated in eight of these patients following 40–45 Gy external beam radiotherapy (EBT). Time/signal-intensity curves were generated and the average maximum signal intensity increase over baseline (SI-I) and rate of uptake over time in two regions of interest within the tumour were calculated. Tumour oxygenation measurements were performed in all 15 patients using the Eppendorf pO2 histograph system prior to treatment and repeated in eight of the patients following EBT. A pre-treatment punch biopsy was taken and immunohistochemically stained with CD31/CD34 for endothelial cells.

Vascularity was assessed as intratumour microvessel density (IMD) within "hot-spots" and intercapillary distance (ICD) for the whole tumour section.

Results: For the 23 parallel measurements there was a significant inverse correlation between the level of tumour oxygenation (% of values < 5 mmHg) and the SI-I ($r = -0.56$, $p = 0.005$) but not rate of uptake. The level of tumour oxygenation also correlated with tumour vascularity measured as ICD ($r = 0.60$, $p < 0.005$) but not angiogenesis measured as IMD ($r = 0.07$, $p = 0.66$). However, there was no significant correlation between MR perfusion parameters and either IMD ($r = 0.07$, $p = 0.81$) or ICD ($r = -0.24$, $p = 0.39$). Maximum tumour diameter at the time of measurement also significantly correlated with SI-I and the level of tumour oxygenation ($r = -0.65$, $p = 0.001$ and $r = 0.36$, $p = 0.043$ respectively).

Conclusion: The results indicate that MR perfusion imaging may be used to give an indication of the level of tumour oxygenation but not angiogenesis (assessed as IMD in biopsy sections) in cervix tumours. More detailed analysis of the MR perfusion time-intensity curves may produce a stronger correlation with tumour oxygenation thus identifying a relatively simple, non invasive method for selecting patients who might benefit from hypoxic modification.

686 ORAL

Differences in palliative radiotherapy practice within Western European countries

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Purpose: To document variations in palliative radiotherapy practice in different types and sizes of radiotherapy departments, within and across Western European countries, and to analyse the possible impact of health care reimbursement systems.

Materials and Methods: A questionnaire was sent to 565 radiotherapy centres in 19 Western European countries, registered in the ESTRO directory of 1997. Palliative radiotherapy practice in terms of total dose, fractionation and treatment complexity was assessed as well as the local reimbursement modalities.

Results: 198 centres (35%) responded. 30 Gy in 3 Gy fractions is the most frequent fractionation schedule (44%), single fractions and 2 Gy fractions being used in res. 13% and 10% of the centres. The majority of the departments uses shielding blocks and performs isodose calculations in less than 50% of patients (res. 79% and 88%). A positive correlation was found ($p = 0.001$) between the size of the department and the fractionation and complexity of the treatment, larger centres favouring shorter and less complex treatments. The same was found for university centres and fractionation ($p = 0.022$), but not for treatment complexity ($p = 0.378$ and 0.440). Both large and university hospitals show a higher proportion of reimbursement through budget and case payment than through fee-for-service ($p = 0.001$ and $p = 0.001$). Fee-for-service represents an incentive towards more fractions ($p = 0.18$) and more complex treatments ($p = 0.001$ and 0.045). National differences in reimbursement systems are thus reflected in the variations in palliative radiotherapy practice.

Conclusion: Besides factors as clinical evidence and local custom, the nature of the reimbursement system also plays a role in the choice of palliative radiotherapy.

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Oesophageal radiotherapy: Potential for dose escalation by conformal techniques

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Purpose: To evaluate the reduction in radiation dose to normal thoracic structures through the use of three-dimensional conformal radiotherapy techniques in the treatment of oesophageal cancer, and to quantify the potential for dose escalation.

Methods: Four different CT-derived treatment plans were created and compared for each of ten patients. A two-phase treatment with conventional straight-edged fields and standard blocks (CV2), a single-phase conformal plan (CF1), a two-phase conformal plan (CF2), and a three-phase conformal plan where the third phase was delivered to the gross tumour only (CF3), were considered for each patient. Treatment plans were assessed using dose-volume histograms and normal tissue complication probabilities (NTCPs) for lung. Escalated dose levels were determined, which would increase tumour control probability (TCP) without increasing the mean lung dose.

Results: Technique CF2 reduced the volume of lung irradiated from 19.7 ± 11.8% (1 SD) to 17.4 ± 12.2% ($p = 0.009$), and reduced NTCP from 2.4 ± 4.0% to 0.7 ± 1.6% ($p = 0.02$). For 48 Gy spinal cord tolerance, technique CF2 permitted a target dose of 60.5 ± 2.1 Gy and technique CF3 a prescribed dose of 63.0 ± 2.9 Gy to the target. Technique CF3 increased TCP from 53.1 ± 5.5% to 78.0 ± 3.2%.

Conclusion: Conformal radiotherapy techniques offer the potential for dose-escalation, and could increase local tumour control substantially without imposing increased lung dose.

688 POSTER DISCUSSION

The links between hypoxia, DNA repair, ATP and radiosensitivity: Time for a paradigm shift

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Classical radiobiology and the linear quadratic (LQ) model cannot explain the common clinical experience that approximately 50% of primary solid tumours can be cured with 60–70 Gy, a dose that only causes moderate damage to normal tissue in 5% of patients. Most normal tissues can tolerate only 4–5 decades of cell kill whereas 8–9 decades are needed to eradicate the last clonogenic cell in a tumour. There is no evidence from in vitro studies that all tumour cells are intrinsically more radiosensitive than all normal cells.

We will provide a new and plausible explanation for this anomaly, using the inducible repair variant of the LQ equation. A computer simulation is used to incorporate data showing a major difference in the effect of acute and chronic hypoxia. This is linked mathematically to recent in vitro data showing that the clonogenic survival after 2 Gy (SF2) is directly proportional to the magnitude of cellular capacity for inducible repair (IRR).

Acute hypoxia leads to an increase in radioresistance by a factor of 3. By contrast, prolonged or chronic hypoxia, with or without glucose depletion, leads to sensitisation by causing a loss of the DNA repair capability. This is accompanied by a fall in the levels of cellular ATP. Thus, two opposing effects of hypoxia have been shown. It is pertinent to ask the magnitude of these 2 effects, which of them occurs in human tumours, and whether the two types of hypoxia can be distinguished.

The biochemical loss of the inducible repair ratio (IRR) is potentially much greater than the chemical protection factor of 3. IRR values range from 1 to 25, and are directly linked to intrinsic oxic radiosensitivity (SF2). Intrinsically resistant cells should therefore be most sensitised by chronic hypoxia/ATP depletion. Even after taking account of the chemical protection factor of 3, the chronically hypoxic cells can be up to 8 times more sensitive than well oxygenated cells. We predict they may actually be the reason why tumours can be cured. This represents a complete paradigm shift.

Our quantitative simulations show that a therapeutic window can never be predicted by the simple LQ model, if we assume that all hypoxic cells are equally resistant. We show however, that using the LQ/IR variant, the clinical observation can be matched if all cells are relatively resistant (the SF2 is about 0.8) and the chronically hypoxic fraction is about 50%.

Current predictive assays for SF2 and hypoxic fraction do not distinguish betwen acute and chronic hypoxia, nor do they take account of the link between the SF2 and IRR values. Predictive tests have shown a wide range in radiosensitivities in both malignant and normal cells, from 0.1–0.9. This relates to clinical radiosensitivity in rank order, but gives rise to unreasonable predictions using the LQ model. Doses of 20 to 400 Gy (in 2 Gy fractions) should be needed to eliminate 9 decades of cells for these SF2 values. In practice all these tumour types show some fraction of cures with doses of 60–70 Gy.

The anomaly between classical radiobiology and clinical knowledge can be explained by the new LQ/IR model if acute and chronic hypoxia are considered separately and SF2 is directly linked to the loss of repair capacity in chronic hypoxia. The use of phosphorus NMR to monitor energy charge depletion via ATP and PI may be a better predictor of clinical outcome than either SF2 assays or hypoxic fraction. estimates.