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## Renal toxicity after total body irradiation

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**Purpose:** To evaluate the incidence of renal dysfunction after total body irradiation (TBI) using the protocol developed at the Transplant Unit, Royal Adelaide Hospital, South Australia.

**Methods:** Between July 1990 and February 1997, 64 patients of median age 40 years, with malignant haematological conditions, Ewing's sarcoma and neuroblastoma received TBI as part of their conditioning regimen with high dose chemotherapy prior to allogeneic bone marrow transplant. All patients with normal renal function at commencement of treatment were included in this study. Conditioning included high dose Cyclophosphamide (CTX) alone (39), CTX with Melphalan (15), high dose Melphalan alone (4), high dose CTX with Busulphan (3),high dose Melphalan with Busulphan, or high dose VP16 with CTX (1). All patients recieved 12 Gy in 6 fractions prescribed to the highest lung isodose (corrected for lung transmission), treating twice daily in 3 consecutive days, at a dose rate of 7.5 cGy/min, using CT scan planning; renal shielding was not utilised. All patients received Acyclovir, Cyclosporin and Amphotericin. The blood pressure of each patient prior to transplant was normal in all patients except in 5, where this was elevated. Renal dysfunction was assessed based on serum creatinine levels measured at the start of TBI, at the end of TBI, 6 months following completion of treatment, at 12 months and at 18 months. The influence of chemotherapy, antibiotics, antifungals, antivirals, infection, hypertension and graft versus host disease (GVDH) on TBI related renal dysfunction was also assessed.

**Results:** In only 4 patients did renal dysfunction deteriorate by the end of TBI. Of these serum creatinine levels normalised within 6 months in 2 patients. The other 2 patients died secondary to multisystem failure as a result of infection. At respectively 6, 12, and 18 months, none of the surviving patients recorded elevated serum creatinine levels. Death secondary to renal dysfunction was only recorded in 1 patient, with multiple myeloma, who succumbed to widespread systemic disease progression. There was no correlation between TBI related renal dysfunction and the development of GVDH, hypertension, type of chemotherapy or antibiotics used.

**Conclusion:** A dose of 12 Gy at 2 Gy per fraction, delivered in 3 days, did not result in renal dysfunction in the patients studied, up to 18 months after completion of TBI.

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## Overcoming mutant p53 with hypoxic cell radiosensitizer, PR-350

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**Purpose:** Tumor hypoxia is common and often associated with resistance to chemotherapy and radiation therapy. PR-350, 2-nitroimidazol nucleoside analog hypoxic cell sensitizer, is now in the way of phase I/II clinical trials combined with conventional radiotherapy or IORT in Japan. The p53 status also has a dramatic effect on tumor response to irradiation. PR-350 can sensitize not only wtp53 cells but also mp53 cells to irradiation. Hypoxic fraction (HF) in tumors is the critical factor in evaluation of the efficacy of hypoxic cell sensitizers. In this study, HF and sensitizer enhancement ratio (SER) of PR-350 were evaluated in solid tumors with different p53 status.

**Materials & Methods:** The human squamous cell carcinoma, SAS/wtp53 and SAS/mp53, with identical genetic background except for the p53 status were used in this study. Irradiation was given locally when tumors, growing subcutaneously, became 50-100 mm3 in their volume. Tumor growth delay time and cure rate were obtained to compare the effects. The hypoxic marker pimonidazole was used to measure tumor hypoxia.

**Results:** SER of PR-350 in wtp53 cells was superior to that in mp53 cells in vitro. Differently from the results in vitro, the magnitude of sensitization of PR-350 seemed to be bigger in SAS/mp53 than in SAS/wtp53. Cure rates at 110 days after treatment of SAS/wtp53 (saline), SAS/wtp53 (PR-350), SAS/mp53(saline) and SAS/mp53(PR-350) were 55, 60, 40, 50%, respectively. Tumor hypoxia was evaluated in three different growing conditions; (a):intra-tumory with sufficient oxygen and nutrient supply, (b):subcutaneously (normal condition), (c):subcutaneously under inferior circumstances (tumor growth time became longer). When tumors were 50-100 mm3 in their volume, HF increased in inverse relation to oxygen supply; HF(c) > HF(b) > HF(a). In good growing conditions(a), HF was almost same between SAS/wtp53 and SAS/mp53. In subcutaneous growing conditions(b), where SER of PR-350 was obtained, HF/SAS/mp53 was 1.6 times bigger than HF/SAS/wtp53. This difference was amplified in the condition (c), that was 1.83.

**Conclusion:** The resistant response of mp53 tumors to irradiation in comparison with wtp53 tumors might be attributed to the different HF between them as shown in our results. Fortunately, PR-350 can overcome this disadvantage of mp53 tumors.

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## Multicellular megacolonies of tumour cells can be useful experimental model for fractionated radiotherapy

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**Purpose:** For studying an influence of fractionation regimens or radiomodifying agents on tumour response, the transplantable solid tumours are the best model. However, using plenty of animals in a such experiments bears some objection for ethical reasons. The multicellular megacolonies of tumour cells in vitro can in some respects replace the animal tumours. The aim of our study was to evaluate an effectiveness of two different fractionation regimens on clonal regrowth, cellular damage and cell cycle redistribution in megacolonie's system.

**Materials and Methods:** Murine SCC cell line AT478 and human lung adenocarcinoma, A549 growing as megacolonies (ca. 1cm in diameter) were used. Conventional fractionation, CF (2Gy/fr, 5day/week) and continuous accelerated irradiation, CAIR (2Gy/fr,7day/week) were applied up to total doses 20-80 Gy.

**Results:** TCD50 estimated on the basis of clonal regrowth were 47 Gy (CAIR) vs 56 Gy (CF) for murine and 56 Gy vs 68 Gy for human lines. TCD50 estimated for single dose, unexpectedely showed higher radiosensitivity for human cells (18 Gy) than for mice (21,6 Gy), suggesting that alpha/beta for adenocarcinoma must be higher. Flow cytometric analysis performed on AT478 megacolonies irradiated with CF and CAIR up to the same dose, 22 Gy, did not show significant differences in cell cycle distribution. However, it was observed that this tumour line contains two aneuploid populations (DI=1.96 ~92%, and DI=1.3 ~8%) and after two day-break in conwentional scheme this near-teraploid population increased up to 97%. It may be more resistant population which repopulate during the break. Cellular damage estimated on the basis of morphological criteria as apoptosis, necrosis and micronuclei indicated higher level of damage, particularly apoptosis frequency, in CAIR than in CF.

**Conclusion:** If some cells can be adapted to grow as multicellular megacolonies, they may serve as useful model for radiobiological studies, specially concerning fractionation effects.

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## Whole brain radiotherapy for cerebral metastases: relation between survival and primary tumour site in 110 cases

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**Purpose:** The discovery of cerebral metastases (CM) modifies the prognosis of patients presenting a cancer. We present a retrospective study of 110 patients treated in the Centre Antoine Lacassagne in Nice, having presented single or multiple CM treated by surgery and/or radiotherapy. The purpose of this study was to obtain a description of the population presenting this kind of pathology and an overview of the relation between primary tumor site and survival.

**Methods and materials:** 77 men and 33 women presenting CM from September 1998 to December 2000 were analysed, the average age was 62 years [36-86]. Treatment consisted of: 1) a complete surgical resection (21%), 2) a partial resection or biopsy (5%), 3) an exclusive radiotherapy of the whole brain (74%). All patients received whole brain irradiation (WBI). Total doses ranged from 18 to 40 Gy, administered with 2 to 6 Gy. per fraction. Approximately 2/3 of the patients received 30 Gy. in 15 fraction. The localization of the CM was supratentorial in 30%, infratentorial in 30%)