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BIOLOGICAL EFFECTS OF CHANGING THE DOSE-RATE - A STUDY OF CLINICAL OUTCOME

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In 1978 at the Christie Hospital preloaded radium applicators for intracavitary therapy of carcinoma of the cervix were replaced by a remote afterloading technique. The prime motivation for this was to reduce the dose to the staff, but also to decrease the treatment time. Due to the decreased treatment time and increased dose rate the treatment would be more acceptable to the patient, reduce the risk of the applicators becoming displaced during the irradiation, and allow efficient use of the equipment. The decision meant a dose rate increase from 0.53 Gy per hour to about 1.7 Gy per hour. Stages Ib and IIa cervix carcinoma have been treated at the Christie Hospital for many years by intracavitary therapy alone. The optimal prescription for these treatments with radium (75 Gy to point A in two equal fractions over 10 to 14 days) had been established in an early study which suggested that there was very little difference in the clinical outcome over a moderately large range of prescribed dose. This together with the fact that a small increase in morbidity may be better than an increased recurrence, led to treatments at a dose level only slightly less than that previously used. In the following clinical trials five different dose levels were used at the higher dose rate. The results of these trials have now been analysed in terms of primary tumour control and treatment related morbidity, and fitted to a dose response model to show the changes in both complication and local control rates as a function of dose. The result is compared with local control and morbidity obtained with the low dose rate system. Based on the treatment outcome and complication data the optimal dose for the new treatment modality is determined. It is slightly lower than with radium but with an increase in morbidity. To improve the treatment and maintain the low complication rate with radium either more than two fractions are needed or a lower dose rate has to be used.

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DOSE-RATE EFFECTS IN BRACHYTHERAPY

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The principal reasons for choosing interstitial or intracavitary radiotherapy in preference to external-beam treatment relate to dose delivery and dose distribution rather than to radiobiology. But the question of whether low dose-rate irradiation itself carries a therapeutic advantage is an interesting one. As dose rate is lowered from rates of few gray per minute as used in most external-beam radiotherapy, various biological processes modify the amount of damage produced in tumours or normal tissues. Down to ≈ 2cGy/min *repair* is the dominant process; below 2cGy/min *repopulation* becomes increasingly important and *reoxygenation* may occur in tumours. Below 2cGy/min cell survival curves tend to be almost straight; their steepness, however, varies considerably from one tumour cell line to another. Calculations of the level of cell killing at different distances from an implanted source show that the probability of tumour eradication has a cliff-like behaviour; the distance from the source at which tumour control fails depends critically on the steepness of the low-dose-rate survival curve. Dose-rate effects down to 2cGy/min are well described by iso-effect formulae based on the Incomplete Repair model. High dose rates are equivalent to the use of a large dose per fraction in multifraction treatment and will tend to produce increased late normal-tissue damage. This will be mitigated by the relatively small irradiated volumes of brachytherapy.

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Low dose rate in gynecological intracavitary brachytherapy.

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Endocavitary brachytherapy (BT) is characterised by both a marked dose and dose rate gradient as a function of distance from the sources. The ICRU report 38 defines as *low dose rate,* any dose rate lying between 0.4 and 2 Gy/hour reported on the 60 Gy isodose. Experimental studies *in vivo* and *in vitro* have taught us that the effect of an decrease an increase in the dose rate of ionising radiation varies from one tissue to another. The sparing effect of low dose rate is particularly effective on *late responding tissues* such as rectum, bladder and sub-mucosa which are indeed the dose limiting tissues in gynecological BT. On the other hand, since treatment is given in a few days, the effect of tumor cell repopulation during treatment is minimised. In other words, low dose rate irradiation *increases* the differential effect between late responding tissues and tumors. In the clinical literature, there are some retrospective studies and one randomised trial comparing two low dose rate regimens (0.4 and 0.8 Gy/h) in cervix cancer BT (Lambin et al., Int. J. Radiat. Onc. Biol. Phys., 25, 405-412, 1993). These data suggest that increases in dose rate in the low dose region, result in higher incidences of complications, while there is no significant influence on the local tumor control. There is therefore, reassuringly, good agreement between the radiobiological and clinical data on the effect of dose rate on both normal tissues and tumors.

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CLINICAL EXPERIENCE OF CHANGING DOSE RATE.

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The introduction of an LDR caesium system to the Christie Hospital in 1978 has been followed by a series of controlled studies designed to establish optimum dose rate correction factors when the dose rate itself was allowed to rise from 53cGy/hr to Point A to 140-180cGy/hr. From 1982 to 1985 228 patients were treated for small volume early carcinoma of the cervix utilising intracavitary therapy alone with dose rate corrections of -12.5% and -19%. Analysis of the mature 5 year results demonstrated no significant difference in 5 year survival (P=0.48), central pelvic control (P=0.21) and morbidity (Grade 2-4 Franco-Italian Glossary) between the caesium treated patients and patients treated by the radium technique. Because of changes in applicator design changes in dose distribution did inadvertently take place in changing between the two systems. The optimum "dose rate" correction factor lies in the range 10-20% and is a System rather than a pure radiobiological correction factor.

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CHANGING DOSE RATE IN LDR INTERSTITIAL THERAPY. Mazeron J.J., Centre des Tumeurs, Hôpital la Salpêtrière, 75651 Paris cedex, France.

The effect of dose rate on cell survival has been demonstrated *in vitro* on cells irradiated at continuous low dose rate. R. PATERSON recommended, in 1952, that dose should be adjusted to treatment duration, in clinical practice. However, this effect of dose rate was not confirmed clinically. Analysis of series of 398 adenocarcinomas of breast treated at Henri Mondor Hospital by a combination of telecobalt (45 Gy / 5 weeks) and Iridium 192 (37 Gy) showed a significant relationship between dose rate and local control (increasing from 60% to 84%, at 15 years, for dose rates increasing from 0.3 to 0.9 Gy/h). Analysis of 279 squamous cell carcinomas of the oral cavity treated at Henri Mondor Hospital definitively with Iridium 192 (60-70 Gy, 0.3-0.9 Gy/h) led to a number of conclusions : First, dose rate is significantly related to local control and necrosis. Second, lowering dose leads to a decrease in local control (independent of dose rate), and lowering dose rate leads to a decrease in necrosis (independent of dose). Third, the best compromise to cure patients without complications is to deliver relatively high dose (65-70 Gy) at relatively low dose rate (0.3-0.5 Gy/h). Fourth, using R. PATERSON's recommendations, a reduction in dose decreases local control without decreasing necrosis rate. However, dose rate modification can lead to a decrease in necrosis without decrease in local control. In conclusion, the study shows that dose rate has an effect on clinical results ; decreasing dose rate produces an increase in the differential effect of radiation on malignant and normal tissues. To maximize local control and minimize complications, we recommend treatment with a relatively high dose at a relatively low dose rate. Dose rate can be altered by modifying either linear activity or intersource spacing (in the range of 0.9-2 cm).

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PULSED DOSE RATE BRACHYTHERAPY - SPECIAL REFERENCE TO HEAD & NECK CANCER

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Brachytherapy has been used routinely in the past for cancer in the Head and Neck, mainly by using low dose rate (LDR) techniques. In recent years HDR remote controlled afterloading technology dramatically changed the horizon of brachytherapy. However, with introduction of HDR afterloaders the radiobiology of tumor response and normal tissues effects changes; if anything, HDR is certainly "less permissive" regarding normal tissue tolerance. Pulse Dose Rate (PDR) brachytherapy has been suggested to deal with this radiobiological dilemma. To investigate the clinical feasibility of new fractionation regimes in brachytherapy, as of August 1990 we embarked on a pilot study for cancer of the Head and Neck. All H & N cancer patients eligible for brachytherapy in the DDHCC were treated by either the microSelectron HDR ("fractionated HDR regime", i.e. a fraction size of 3 Gy, twice daily with an interval of 6 hours between fractions) or the microSelectron PDR ("pulsed-dose-rate regime", i.e. a fraction size of 1-1.5 Gy, 8 times per day with an interval of 3 hours between fractions). For the fractionated HDR and PDR calculations, the LQ-model is used, taking into account incomplete repair of sublethal damage in the (limited) time between fractions and also taking into account the (finite) duration of each radiation fraction. This paper will deal with preliminary results in the DDHCC on 113 patients with cancer in the H & N using fractionated HDR- and PDR brachytherapy through interstitial or endocavitary techniques.