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RADIOBIOLOGY IN CLINICAL RADIATION THERAPY - PART II - CURRENT PRACTICE AND NEW HORIZONS

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The multifraction regimens used in conventional radiotherapy were developed empirically, but can be understood in terms of radiobiological principles. Dividing the dose into many fractions reduces biological effectiveness due to repair of sublethal damage; this occurs in both tumors and normal tissues. Fractionation allows re-oxygenation to occur in tumors and so increases the effectiveness of a given total dose. Fractionation also leads to sensitization by reassortment of cycling tumor cells into radiosensitive phases of the cycle. Laboratory research also provides a rationale for modifications of existing fractionation protocols. The dose response relationship for late responding tissues is more "curved" than for acute or early effects. Consequently the use of multiple fractions allows a greater separation of early and late effects in normal tissues. This has led to the introduction of hyperfractionation and accelerated treatment. Both involve two treatments per day (BID) but based on quite different rationales. The limitation of protraction is cell proliferation in the tumor, which may be accelerated as the tumor shrinks. Measurements of cell kinetics can identify fast growing tumors that may benefit from accelerated treatment.

Hypoxia was early identified as a cause of resistance to cell killing by x-rays. This led to the development of electron affinic compounds as radiosensitizers of hypoxic cells. The new trend is the development of bioreductive drugs that are specifically cytotoxic to hypoxic cells. Neutrons were initially introduced, too, in an attempt to overcome the perceived problems of hypoxia, but clinical trials now are based on the premise that neutron RBE values are larger for slowly proliferating tumors. Heavy ions combine the superior physical dose distributions with the biological advantages of high LET.

An important new horizon is the development of predictive assays to individualize treatment, and to identify patients that might benefit from new treatment strategies. Some assays predict individual patients who may be sensitive or resistant to radiotherapy by measuring the response of a sample of tumor cells to a dose of 2 Gy. Other assays are designed to detect the presence of hypoxic cells. The most practical predictive assay developed so far is the measurement of Tpot to identify rapidly proliferating tumors.

Hyperthermia offers exciting possibilities as an adjunct to radiation. The potential advantages are: S-phase cells which are resistant to x-rays are sensitive to heat; cells at low pH or nutritionally deprived are sensitive to heat and these are most likely to be found in tumors; heat destroys tumor vasculature; areas treated to tolerance with x-rays can be retreated with heat without producing normal tissue necrosis. The limitation of hyperthermia would appear to be the engineering of devices to produce uniform regions of elevated temperature at depth in a patient without distortion from air cavities or bones.

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STRATEGIES FOR PREVENTION AND SYMPTOM MANAGEMENT OF RADIATION THERAPY-RELATED TOXICITIES

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The predictable short-term morbidity of full treatment courses of curative or palliative radiation therapy (RT) interferes with both our ability to deliver optimal treatment and with the quality of life of our patients. There is a growing literature citing the deleterious effect of unplanned RT treatment interruptions on tumor control. The purpose of this course is: (1) to identify strategies which reduce the acute morbidity of an RT course without compromising adequate tumor treatment; (2) to clarify optimal management of RT-related symptoms both to prevent unnecessary treatment interruptions and to avoid undue patient suffering.

Strategies for reducing normal tissue toxicity include: (1) improved tumor localization, including the use of three-dimensional computerized treatment planning and appropriate use of contrast agents and radio-opaque surgical clips; (2) improved normal tissue localization through such techniques as the use of small bowel contrast and lung perfusion scanning; (3) the use of altered fractionation RT; (4) optimal integration of systemic chemotherapy and RT; and (5) the investigative use of radiation protection agents, such as ethyl or colony stimulating factors.

Discussion of symptom management will include information on: (1) such pre-treatment corrective measures as pain control and nutritional supplementation; (2) the preventive use of anti-microbial agents; and (3) the therapeutic options for upper aerodigestive mucositis, gastrointestinal and genitourinary treatment toxicities, and moderate to severe skin reactions. The common toxicity criteria grading system adopted by the Cancer Therapy Evaluation Program (CTEP) in 1988 will be reviewed, as well as the recently revised Radiation Therapy Oncology Group (RTOG) toxicity grading system.