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Fractionation in Radiotherapy

RADIATION can induce partial and complete remissions and achieve cures in a wide range of tumour types. These clinical responses may reflect intrinsic sensitivity, as in lymphomas or seminomas. However, in most cases, and specifically in epithelial tumours, the difference between normal tissue and tumour sensitivity may be small. In such a situation the total radiation dose, the manner in which the dose is administered and the dose distribution within the patient are critical. In practice the total dose of radiation is subdivided into fractions to increase the therapeutic ratio, by taking advantage of the superior ability of normal tissues compared with some types of tumour cells to recover from radiation damage between fractions. Conventional fractionation, which has been derived empirically over many decades, usually employs 2 Gy fractions given daily 5 days each week.

It has been known for many years that modification of fractionation schedules can lead to substantial changes in the tolerance of normal tissues and that important differences exist between different normal tissues. It is now clear that slowly proliferating tissues are more susceptible to changes in fractionation than tissues with a rapid turnover. An expression of this is the fact that late reactions are more influenced by changes in fractionation than acute early reactions.

The important question is whether different fractionation schedules may also have a different impact on the probability of tumour control. Although more data are required to provide an answer it is probable that modified fractionation schedules will increase the therapeutic ratio in a number of clinical situations. Unlike normal tissues, available animal tumour models have a vastly different cell proliferation pattern from human tumours, making them much less suitable for predictive studies on fractionation effects. Thus, while recent data have provided a reasonably good basis for the selection of fractionation schedules associated with improved tolerance of normal tissues, it is only now that data on the respective repair capacities of different human tumour types are being collected.

When the study by Jean-Claude Horiot and colleagues (including myself) on modified fractionation for head and neck cancer (p) was designed and initiated, only the general principles were known. The trial was based on the hypothesis that a schedule employing a larger number of fractions of radiation would preferentially reduce late reactions compared with those observed in rapidly proliferating tissues. This provided the rationale for a study of hyperfractionation in head and neck cancer where the critical tolerance limit is late fibrosis and possible necrosis, and where it is assumed that the tumours are rapidly dividing cell populations. In the study, the use of small fraction sizes allowed a higher radiation dose to be given, with the reasonable expectation that for equal levels of normal tissue damage compared with conventional fractionation, the antitumour effect would be increased. The preliminary results of the study appear to confirm this.

It is instructive to look at how long a study of this type took. Many years were required for the inclusion of an adequate number of patients fulfilling the entry criteria, and for the post-treatment observation time necessary to obtain reliable data on local control and survival. This underlines the importance of collecting more experimental data on which to select fractionation schedules for investigation in clinical trials, and stresses the need for wide multicentre participation in such studies. Small, institute-related pilot studies are often valueless for long-term analysis due to insufficient numbers of patients, while multicentre studies with an increased level of support might be concluded over a shorter period.

It would be unrealistic to anticipate dramatic short-term improvements; rather the aim should be to construct with care, and step by step, a long-term strategy for the optimal application of radiation, which remains one of the most powerful and polyvalent cytostatic agents. The temptation to skip intermediate steps in the hope of achieving a rapid advance has all too often proven to be a setback in oncology. It is hoped that the present results will encourage further carefully designed studies that attract wider multicentre participation.

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