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# Developments in Radiotherapy

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## INTRODUCTION

1995 SEES THE 100th anniversary of the discovery of X-rays and the birth of the disciplines of radiology and radiotherapy. Since the 1960s, a number of technology based revolutions in radiobiology, therapy machine design, computers and imaging have offered opportunities in radiotherapy which we are now challenged to explore, optimise and integrate into the overall management of patients with cancer. This summarises some of the achievements and possibilities brought about by these advances.

## IMAGING

Information from CT, MRI and ultrasound is used to delineate tumour and define normal structures, whilst functional imaging (PET, SPET, MRS) can add further information regarding the viable, proliferative and responsive parts of the tumour. Potentially, all this information can be integrated into radiotherapy planning [1], but only CT scanning is established in radiotherapy practice. In 1983, Dobbs and colleagues [2] examined 320 patients scheduled for a radical treatment, comparing CT generated plans with those derived from best conventional methods. They found that 29% of patients had "inadequate coverage" of the tumour. Results of this kind led to the rapid adoption of CT planning techniques. However, no randomised trial has ever been performed to see whether clinical outcome is improved.

CT images comprise a matrix of relative attenuation coefficients which can be readily converted to relative electron densities and hence used for dose calculations. Modern computers allow this matrix to be represented as a 3D image which can be viewed from any orientation. This can lead to better tumour coverage and, in particular, the 'Beams Eye View' provides opportunities for accurate beam placement and shaping. Fast and sophisticated 3D planning systems allow us to use unconventional non-coplanar planning techniques with three or more individually tailored beams to create 3D volumes unique to each tumour (i.e. true conformal therapy). Such opportunities, however, demand new methods of treatment plan assessment, such as dose volume histograms, 3D dose surfaces or volumes of regret [3].

Although MRI has advantages over CT in many situations, the lack of electron density data and problems of distortion have delayed the incorporation of MRI into radiotherapy planning. We and others have achieved this by adapting conventional scanning protocols, and developing image co-registration systems. These methods have been used in the radiation planning of brain tumours [4].

## DOSE ESCALATION

It has been shown clinically that, for some tumours, there exists a dose–response effect. The dose which can be delivered to a tumour is not normally limited by the tumour itself, but by the dose experienced by neighbouring tissues. Dose volume effects are also important. It follows that if a method is devised to reduce the volume of normal tissue irradiated, or alternatively to reduce the dose to the same volume of normal tissue, then it might be possible to increase the tumour dose. Conformal therapy [5] and implantation [6] are examples of the former strategy, whilst stereotactic radiotherapy [7] represents the latter.

Conformal therapy has concentrated largely on pelvic tumours where phase I studies in prostate cancer have safely increased tumour doses beyond 70 Gy [Mijnheer, personal communication, 1994].

Both implantation and external beam therapy have found new application in the treatment of brain tumours through the adoption of stereotactic techniques. Stereotactic external beam therapy has an established role in AVM and possibly in certain small brain tumours, however, the value of these techniques in the wider management of cancer remains to be determined.

## ALTERED FRACTIONATION SCHEDULES

Radiobiological research has clearly shown differences in the way early responding tissues (including tumours) with high $\alpha/\beta$ ratios and late responding tissues with low $\alpha/\beta$ ratios are affected by changes in radiation fraction schedules. Some, which depart from the conventional 2 Gy fraction 5 times a week, have the potential for improved local tumour control and reduced late tissue morbidity [8].

Pure hyperfractionation schemes deliver the same (or greater) radiation dose in the same time but using a larger number of smaller fractions. This approach exploits differences in repair capacities and cell cycle effects between tumours and late responding tissues. Both of these act preferentially to spare damage in late responding (normal) tissues which is frequently dose limiting. Trials of this approach, such as that reported in oropharyngeal cancer by Horiot and colleagues [9], have shown that the final total dose can be safely increased (by 14% in this report) without increase in late radiation damage and with improved local control.

Pure accelerated fractionation schemes deliver the same or a lower radiation dose but in a shorter period of time and with a similar dose per fraction. The rationale in this case is to overcome repopulation effects in rapidly cycling tumours as has been discussed extensively elsewhere [10].

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CHART or Continuous Hyperfractionated Accelerated RadioTherapy seeks to combine both aspects, and unlike most other regimes, does so by treating 7 days a week. In pilot studies at Mount Vernon hospital [11], highly significant improvements in local control compared to historical controls have been demonstrated in patients with head and neck cancer (58% versus 28% at 3 years) and in survival for NSCCL (29% versus 12% at 2 years). On this basis, it was decided to mount a multicentre prospective randomised clinical trial of CHART (50.4 Gy/36 # / 12 days) compared to conventionally fractionated radiotherapy in head and neck and NSCCL. By July 1994, 852 patients had accrued into the H & N study, 507 into the bronchus study. The results will have major implications for the future of modified fractionation schedules in rapidly proliferating tumours.

## CHEMORADIOTHERAPY

New generation bioreductive compounds have renewed interest in radiation potentiation by chemotherapeutic drugs.

That malignant tumours contain hypoxic regions is not in doubt. Amongst the wealth of evidence demonstrating this are powerful data derived from *in vivo* measurements with polarographic electrodes in cervical, breast and brain tumours [12]. SPET data demonstrate viable cells in these regions which will be three times more resistant to radiation than their oxygenated counterparts. SR4233 is the lead compound of a new generation of bioreductive agents which are selective hypoxic cell cytotoxins. A combination of SR4233 and radiation is a logical one to produce synergistic cell killing in these tumours. This theoretical concept has been demonstrated in animals [13] and the compound has completed first round phase I testing [14]. Viewing hypoxia as an advantage to be exploited rather than an obstacle to be overcome is novel in radiotherapeutic thinking and has considerable potential.

## TARGETED RADIOTHERAPY

Systemic radiotherapy is an established technique, but recent attempts to treat patients with targeting agents, such as radiolabelled monoclonal antibodies, have failed largely because of their lack of specificity and possibly because the wrong isotope strategy was used. Targeted therapy is only likely to be successful if the underlying physical principles are understood and appropriately applied. This important principle is illustrated in the following example.

Iodine-131 is a relatively long range β emitter (mean range ≈ 600 μ) of low LET. It therefore relies for effective cell killing on crossfire effects. Paradoxically, therefore, given a relatively uniform uptake into tumours of varying sizes, treatment with $^{131}I$ is more likely to sterilise larger tumours than those of smaller size [15]. This argument fails as the tumours increase further in size and the distribution of the total administered dose of $^{131}I$ is diluted into the large volume. Hence, for a particular dose of a given isotope, there will be an optimal size of tumour for treatment response. The logical extension of this argument is that, just as cytotoxic therapy might comprise combinations of agents, so might radiotherapy. Gaze and associates [16] have piloted a regime combining three radiation modalities; intravenous $^{131}$mIBG, TBI and conventional external beam with high dose melphalan following standard therapy in neuroblastoma and have shown surprisingly long survivals in poor prognosis patients.


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