How to improve effects of radiation and control its toxicity

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Introduction

Radiotherapy is an important contributor to curative treatment of cancer and as the most effective non-surgical treatment modality contributes to 18% of all cancer cures [1] and to 40% of all long term survivors [2]. In the next decade we need to build on clinical advances by optimising all treatment modalities and their combinations.

In order to understand the options for clinical improvements in radiation therapy we need to understand some of the fundamental principles governing the effects of radiation on biological tissues and systems. For simplicity we will concentrate on external beam photons and exclude special forms of irradiation such as electron beams, brachytherapy and high LET irradiation.

The therapeutic index of radiotherapy is a complex function influenced by technical, biological and host related parameters and augmented by the effects of additional stress such as chemotherapy, surgery or unrelated biological insults. Effects on tumours must be considered together with those on critical normal tissues.

Most of the core DNA damage that ionising radiation inflicts is repaired but if it is not it will manifest itself by cell death during subsequent divisions. Therefore the expression of this damage will be related to the magnitude of radiation dose [3], the kinetics of the irradiated tissue and the functional changes caused by cellular depopulation within the irradiated volume.

Tissues respond to radiation damage in broadly two ways [4]:

- Early: proliferating tissues such as gut, skin, blood and most tumours show predominantly acute radiation reactions which are due to cell depletion and can recover by repopulation from cellular reserves. Acute reactions are time limited unless the irradiated volume encompassed the critical organ as a whole. They are poor predictors of the dose limiting hallmark of radiation damage–late toxicity.

- Late: lung, kidney, CNS. In most instances it is the late reactions that are dose limiting, characterised by cell loss and vascular changes causing a spectrum from necrosis to atrophy. Dense fibrosis is the clinically apparent feature. There is no recovery. Clinical relevance of these effects will be determined by the severity, site and volume of tissue affected and may not manifest itself for years.

In clinical practice a course of radiation is defined by the prescribed radiation dose (including homogeneity), schedule of administration (number of fractions and overall treatment time), the volume of tissues irradiated and dose to critical tissues in the irradiated volume [5].

When reporting outcomes (tumour control and toxicity), time of and method of assessment should be stated [6].

Current schedules have been developed largely empirically by careful clinical evaluation of tumour and normal tissue effects. Durable long-term control of tumours is the prerequisite for cure and relates only indirectly to measurements such as tumour response. For safety assessment cohorts of cured patients need to be followed for a long time and for stochastic effects such as carcinogenesis, for life.

The final issue is the Quality Assurance of the multi-step and multiprofessional process of clinical radiotherapy which ensures that the delivery is within specified tolerances of accuracy for dose and target [7].

The therapeutic ratio of a radiation course can be altered by manipulation of any of its parameters and/or addition of other therapy.

Radiation dose and fractionation

The classical parameters of radiation dose are the dose specified in Gy, fractionation schedule and overall treatment time.

Classical radiation schedules use once daily (5×
per week) fractionation of 1.8–2.5 Gy over a period of 4–6 weeks and a total dose of 50–65 Gy.

Hyperfractionation uses larger number of smaller fractions which reduces late normal tissue effects, but protracted treatment time leads to loss of tumour effect [8] through repopulation. Accelerating treatment by shortening the overall time achieved by administering more than one fraction per day increases biological effectiveness on tumour and acute reacting tissues. The interfraction time interval is important for repair of normal tissue damage [9]. The predominant effect on normal tissues will be an increase in acute reactions.

One of the recently developed schedules exploiting these mechanisms to clinically valuable effects is continuous hyperfractionated accelerated radiotherapy (CHART) [10].

Hypofractionation uses reduced number of fractions of larger individual size. This approach leads to increased late tissue morbidity and is reserved for palliative treatments where convenience to patients is the prime concern.

Better understanding of tumour and normal tissue biology has led to the development of different schedules, aimed at exploiting critical differences between tumours and normal tissue and widening the therapeutic ratio [11].

The main types of schedules are summarised in Fig. 1.

Fig. 2 shows the effects of changing dose per fraction on tumour and acute and late reacting normal tissues.

**Treatment volume**

The development of 3D conformal or Beam Intensity Modulated radiotherapy techniques brings a new dimension by allowing a high and precise radiation dose delivery to radiologically well defined volumes. By limiting the dose to surrounding tissues substantial dose escalation is possible [12]. These planning systems allow for accurate determination of dose delivered to specified volumes of critical normal tissues such as lung and therefore evaluation of treatment effects.

These technical advances bring their own problems. By reducing the safety margin around the target patients and organ immobilisation, reproducibility and sophisticated imaging become fundamental requirements. Knowledge of the degree and distance of subclinical tumour infiltration around radiologically and clinically apparent mass may not be available and protocols using new and tight margins must be critically reviewed for marginal recurrences before they are accepted as safe.

Complex planning and treatment protocols are time consuming and resource intensive and need a sophisticated departmental organisation including quality assurance and are commonly reserved for research setting. The challenge will be making this approach more widely available.

**Combined modality treatments**

The interactions of chemotherapy and irradiation are complex and not always beneficial. When designing new combined modality treatment schedules the investigators must be aware of the potential for harm as well as benefit and best progress is made by joint working of a multidisciplinary team aware of the constraints and advantages of each individual treatment modality.

The classical theoretical concepts such as spatial co-operation, independent toxicity, reduction in normal tissue injury and enhancement of tumour response first outlined by Steel [13] continue to provide a useful framework.

Improved understanding based on laboratory findings as well as careful analysis of available clinical data can inform the process of schedule development and testing.
Schedules designed to improve local effects of radiotherapy (radiosensitisation) use prolonged time of common exposure between drug and radiation. Repeat small doses of chemotherapy or continuous infusion are administered with timing dependent on the pharmacokinetics and cumulative toxicity of the drug used. Platinum compounds 5-FU, Taxans and gemcitabine have all been used in this approach. All lack specificity for tumour selectivity and this necessitates dose reductions which will impair the effectiveness of this approach against metastatic disease. For enhanced cytoreduction at the primary as well as metastatic sites, both treatment modalities are used at their maximum tolerated doses (MTD).

The MTD concepts for chemotherapy and irradiation vary depending on timescale and selection of organ at risk. Chemotherapy dose is frequently limited by acute side effects such as haematological toxicity and recovery.

For radiation, acute side effects become dose limiting only in high dose, hyperfractionated and accelerated regimens [10] or in combination with chemotherapy.

Both sets of toxicities are augmented by patient related factors such as PS, underlying co-morbidity and may exhibit some organ specificity.

Sequential administration of chemotherapy and irradiation remains the easiest practical schedule which allows full doses of each treatment modality to be given safely. It allows evaluation of tumour response to each therapeutic component and use of this information in the assessment of treatment efficacy and determination of prognosis for individual patient. The disadvantage is the single agent exposure which reduces drug radiation interactions, increasing sensitivity [14] or resulting in useful kinetic effects [15].

The way forward

The clinical challenge now is to design, execute and evaluate studies which could test these concepts in practice. Radiation schedules and chemotherapy agents with individually well defined toxicities and efficacy should be combined in schedules designed to test the concepts of synergism or at least additivity for both tumour and normal tissue effects. These effects can span a spectrum of potentiation in both the tumour and normal tissues. In many situations formal phase I studies will be necessary in order to determine the dose and schedule producing optimal therapeutic ratio. The critical toxicity endpoints may well be delayed and sufficient follow up needs to be built into the evaluation if they are to be assessed. Such a programme can be cumbersome and protracted. It is therefore not surprising that clinicians are keen to progress directly to more practically usable schedules. The danger is that unexpected toxicity will outweigh small efficacy gains and that a potentially valuable combination may be discredited by choice of inappropriate dose or schedule. The value of intergroup collaborations in sharing the burden and benefits of rational development and testing is self-evident.

Outside of research settings it is important to remember that two suboptimal treatments rarely improve the outcome and that combined modality treatment is a team effort where close collaboration and understanding between medical and radiation oncologists is essential for the patients benefit.

References