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Overview

Incorporating Genetic Biomarkers into Predictive Models of Normal Tissue Toxicity

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Abstract

There is considerable variation in the level of toxicity patients experience for a given dose of radiotherapy, which is associated with differences in underlying individual normal tissue radiosensitivity. A number of syndromes have a large effect on clinical radiosensitivity, but these are rare. Among non-syndromic patients, variation is less extreme, but equivalent to a ±20% variation in dose. Thus, if individual normal tissue radiosensitivity could be measured, it should be possible to optimise schedules for individual patients. Early investigations of *in vitro* cellular radiosensitivity supported a link with tissue response, but individual studies were equivocal. A lymphocyte apoptosis assay has potential, and is currently under prospective validation. The investigation of underlying genetic variation also has potential. Although early candidate gene studies were inconclusive, more recent genome-wide association studies are revealing definite associations between genotype and toxicity and highlighting the potential for future genetic testing. Genetic testing and individualised dose prescriptions could reduce toxicity in radiosensitive patients, and permit isotoxic dose escalation to increase local control in radioresistant individuals. The approach could improve outcomes for half the patients requiring radical radiotherapy. As a number of patient- and treatment-related factors also affect the risk of toxicity for a given dose, genetic testing data will need to be incorporated into models that combine patient, treatment and genetic data.

Key words: GWAS; normal tissue; radiosensitivity; radiotherapy; SNP

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

Introduction

Radiotherapy is one of the most effective treatments for cancer [1]. It is needed in the care of about 50% of cancer patients at some time in their illness. As the lifetime risk of cancer for people born since 1960 is estimated to be >50% [2], radiotherapy will ultimately be required for a quarter of the population. It forms a major part of the treatment plan for 40% of those who are cured and is primarily responsible for cure in 16%. Around 60% of patients undergoing radiotherapy are treated with curative intent [3]. The incidence of cancer in the UK is about 331 000 cases per annum [4]; radical radiotherapy is used in around 100 000 patients each year.

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The success of radiotherapy in eradicating a tumour depends especially on radiation dose, which is limited by the tolerance of surrounding normal tissues. Patients treated to the same curative dose vary in the toxicity they experience. A minority have no observable effect, most have clinically mild or moderate changes, and a few suffer serious normal tissue complications that may even be life-threatening. The incidence and severity of normal tissue damage is radiation dose dependent. However, even mild or moderate damage can have a substantial negative effect on patient-reported quality of life and requires consideration. Selection of the appropriate radiotherapy is based on a balance between lowering the dose to keep the incidence of severe normal tissue complications at an acceptably low level and raising the dose to increase the probability of local control. However, at present, this is only carried out on a population level, without the possibility of personalisation based on individual normal tissue tolerance.

Toxicity can be reduced by using advanced radiotherapy techniques, which limit normal tissue doses, especially intensity-modulated radiotherapy [5–13], addressing physical individualisation. All modern radiotherapy includes a substantial component of physical individualisation, which is not yet matched by the biological equivalent. Developments in radiotherapy, including the ability to combine physical and biological individualisation, will make an essential contribution to the Cancer Research UK vision of curing 75% of cancer patients in 20 years' time [14]. This overview addresses the issue of biological individualisation of radiotherapy, which is a goal that should be reached well within this time frame, offering better cure rates with less toxicity for patients with cancer.

Background

The First Descriptions of Individual Variation in Toxicity

The first documented illustration of variation in toxicity after radiotherapy was reported by Holthusen in 1936 [15]. The evidence for individual variation in radiosensitivity led to the development of studies aimed at measuring radiosensitivity to predict a cancer patient's risk of toxicity. The variation was hypothesised to have a genetic basis, even though these efforts pre-dated the development of the necessary genotyping technology to prove this. Initially laboratory measurements of radiosensitivity were developed to attempt to predict normal tissue toxicity. The earliest studies focused on individuals with very severe toxicity, many with heritable syndromes, including ataxia telangiectasia. Fibroblasts cultured from skin samples of such patients were shown to be unusually radiosensitive using clonogenic assays [16–21]. Clonogenic assays assess reproductive integrity, i.e. the ability of single cells to form a colony with a minimum of 50 cells (representing at least five to six cell divisions) [22]. These studies showed a wide range of sensitivity, largely because of the inclusion of cells from patients with genetic syndromes typically associated with DNA damage recognition and repair defects, causing severe clinical and cellular radiosensitivity.

Efforts to Develop Predictive Testing Based on Cellular Radiosensitivity

With the demonstration in the 1980s that there was variation in fibroblast radiosensitivity between cells cultured from individuals both with and without known genetic syndromes [17,23–25], studies were set up to investigate the relationship between cellular and clinical radiosensitivity with the goal of developing a test to predict a patient's likely reaction to radiotherapy. The first studies were retrospective and compared patients who developed severe reactions to radiotherapy with those with no/minimal toxicity. Toxicity was typically relative, with some patients probably not expressing really severe reactions, which presented a problem of discrimination in the clonogenic assay. The results suggested some value in cellular sensitivity testing, but without providing clear proof of a link between cellular and tissue radiosensitivity.

The next step saw several small studies of patients whose toxicity had been quantified more objectively. Each of these showed a correlation between cellular sensitivity and normal tissue response [26–29]. Although the results, individually and collectively, were encouraging, the relationship between cellular sensitivity and normal tissue response could not be replicated in larger studies using the clonogenic assay with fibroblasts cultured from skin samples [30]. Better results were obtained using lymphocytes [31].

As deriving fibroblast lines from skin samples and carrying out the necessary clonogenic assays (in triplicate) takes 6–8 weeks and is labour-intensive, interest moved to investigating more rapid assays that would have greater clinical utility. The main ones studied have been expertly reviewed elsewhere [32] and include: chromosome damage assays, including include the 'micronucleus' and G2 lymphocyte assays; DNA damage, including the 'comet' assay; assessment of apoptosis; the ability of fibroblasts to undergo radiation-induced differentiation; and alteration in telomere length. Combinations of assays have also been tested. Despite considerable effort, none of these methods proved reliable in a clinical setting. An important reason may be that the differences between cells from normal (as opposed to syndromic) patients are rather small, and of similar magnitude to the variability in the assays. Another important reason may be that the response of cultured cells might not be sufficiently comparable with the response of whole tissues, in which the microenvironment could play an important role in radiation-induced damage. Finally, the quality of dosimetry and reporting of clinical toxicity must be well controlled, but in general, studies seeking to correlate sensitivity assays with clinical outcome have addressed these issues.

There is also interest in measuring the expression of cytokines in serum/plasma. A combined two centre analysis of 165 patients with non-small cell lung cancer showed that

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