LECTURE 1

THE GENOMICS REVOLUTION AND RADIOTHERAPY

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The draft sequence of the human genome was published in 2001 with the full sequence becoming available in April 2003. The expansion of knowledge through the Human Genome Project was accompanied by the development of new high throughput technologies and capabilities for the concurrent analysis of a large number of genes or the whole genome. This ‘genomic revolution’ increases the possibility of future personalised radiotherapy based on molecular profiling.

During the 1990s, predictive assay work was dominated by cellular-based assays and involved measuring specific radiobiological phenotypes: tumour and normal tissue radiosensitivity, tumour proliferation and tumour hypoxia. Research in this area has now evolved to investigate high throughput assays, which can be carried out in various clinical samples at the DNA (genome), RNA (transcriptome) or protein (proteome) level. There is a belief that the ability to assess many to all genes increases the probability of developing profiles that predict response to radiotherapy. This view stems from the awareness that not only are the new techniques more comprehensive and have the potential to be more robust than cellular-based assays but also that, after improvements in the technology of radiation delivery have been realised, the key to progress lies in our ability to measure differences in patient biology. To date, the best developed approach for whole genome analysis involves RNA expression profiling.

Gene expression microarrays were first described in 1995 by a group in Stanford. They provide the ability to monitor, rapidly and simultaneously, the RNA expression level of the whole genome. The relevance of RNA microarrays for radiotherapy lies in their use to develop gene signatures that reflect radiobiologically relevant phenotypes and so predict response to radiotherapy. Hypoxia, a key factor involved in tumour radioresistance, has been widely investigated in human cancers. Recently microarray profiling was used to generate gene expression profiles associated with hypoxia. These hypoxia-associated gene signatures were prognostic for cancer treatment outcome in independent datasets. Gene expression profiles are also being developed that reflect other radiobiologically relevant phenotypes such as tumour radiosensitivity and proliferation.

Incorporating biological measurements into a tumour control probability model was shown to increase their prognostic significance. Towards this goal, it is important to explore how to incorporate the new gene signature data within radiobiological models to improve radiotherapy dose prescriptions.
LECTURE 2

RADIOBIOLOGY, RADIOGENOMICS AND RAPPER – HOW CLOSE ARE WE AT BEING ABLE TO PREDICT RADIOThERAPY TOXICITY?

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The existence of individuals with extreme sensitivity to ionising radiation was first realised with the publication of a study showing the hypersensitivity of fibroblasts cultured from a patient with ataxia telangiectasia. This was followed by several reports showing that severely over-reacting patients had hypersensitive fibroblasts. By the 1980s there was increasing evidence for a spectrum of normal cell radiosensitivity within the population, with studies demonstrating significant differences in radiosensitivity of fibroblasts and lymphocytes taken form ‘normal’ donors. It is the 5% most sensitive of these individuals within a patient population that limit the doses that can be safely applied in radiotherapy.

In the 1990s studies were established to test whether normal cell radiosensitivity correlated with the severity of normal tissue damage seen. Several studies showed correlations between fibroblast radiosensitivity and the severity of radiotherapy toxicity, but larger studies failed to confirm the initial findings. Large studies involving lymphocytes, however, did show a relationship between measured radiosensitivity and radiotherapy toxicity. During the second half of the 1990s there were many studies investigating potential rapid assays of radiosensitivity but by the end of the 20th century it became clear that cellular based assays generally lacked the necessary sensitivity and specificity on which to base clinical decisions.

Knowledge of the genetic basis for individual radiosensitivity came from studies investigating rare cancer pre-disposing disorders and led to interest in measuring $ATM$ mutations in relation to radiation toxicity. More recently it has been recognised that multiple cellular pathways are involved in the pathogenesis of radiation-induced normal tissue damage not only DNA damage recognition and repair but also cytokine and inflammatory response genes. Normal tissue radiosensitivity is now regarded as an inherited phenotype, and is considered to be a complex trait dependent on the interaction of multiple genes or gene products. This knowledge has led to interest in measuring genetic variation to predict a patient’s likelihood of developing radiation toxicity (radiogenomics).

Genetic variation is not limited to rate mutations but also includes single nucleotide polymorphisms (SNPs), which account for ~90% of the naturally occurring sequence variation within a population. The success (or failure) of radiogenomics will depend on our ability to design and perform studies with sufficient power to detect real effects. The ultimate goal is to develop genetic profiles that allow individualisation of radiation dose to optimise tumour control while reducing toxicity. RAPPER is a large, UK radiogenomics study testing the hypothesis that SNPs in multiple genes are responsible for individual variation in normal tissue response to radiotherapy. RAPPER was designed to look at ~50 candidate genes but high-throughput genotyping of millions of SNPs is now possible. A genome-wide study requires analysis of ~10,000 patients but has potential to derive a radiosensitivity signature that will identify new genes associated with radiotherapy toxicity.