Teaching Lectures

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Translational research in radiation oncology

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The goal of translational research is to facilitate the introduction of new diagnostics and therapeutics into the clinic from basic advances in technology and biology. For the field of radiation oncology, translation research is positioned well to capitalize on recent advances. In the past decade we have witnessed the complete sequencing of the human genome and an unprecedented increase in our basic understanding of cancer at the molecular level. This has stimulated the development of new drugs developed to target specific biological pathways. The combination of these drugs with radiotherapy has significant potential for improving anti-tumour responses over radiation treatment alone. This philosophy is based on the tenet that although new agents are often highly tumour specific and exhibit very good toxicity profiles, they are unable to kill the 9 to 10 logs of tumour cells required to cure a tumour. Thus, it is possible that promising new therapeutic compounds which could benefit standard therapies may be missed in poorly designed or single therapy trials.

Challenges for translational researchers in radiation oncology are twofold. The first is in making choices about which molecular pathways should be investigated as targets in the clinic. We have a wealth of information regarding genes, pathways, and responses which may be important determinants of therapy. The difficulty is in our ability to determine which of these pathways play important roles in which patients. In radiation oncology, there is a long history of attempting to understand the variables that contribute to failure and these include radiation resistance, proliferation and hypoxia. We now have a much better understanding of the genes and pathways which control these phenomenon and therapies targeting proteins in each of these pathways are being evaluated. Our success in combining new molecularly targeted therapies with radiotherapy in a rational and effective way is contingent upon our ability to identify those tumors which will benefit. Several recent examples suggest that genomic and/or proteomic profiles will allow such 'individualization' of therapy in the future.

The second challenge facing translational researchers is in the design of effective clinical trials which ensure a flow of information from the bedside back to the lab. With the realization that most trials will be negative coupled with the high costs of developing and testing new drugs, it is imperative that trials are designed with a goal to increase our basic understanding of disease. Historically, clinical trials have been the end-step on the development of a new therapy in which the primary goal was simply to determine if the new therapy was better than the old. This approach may have been logical in the past when the method of action of many drugs was poorly understood, but is much less useful today when speaking of drugs designed to target specific molecular pathways. One critical component of new trials is thus collection of biological tissue. In the case of a classical 'negative' trial, this tissue might be used to identify biological differences (genetic profiles) which identify a subset of patients who can benefit from the new treatment. Similarly, in the case of a 'positive' trial this tissue might be used to identify those patients who do not benefit and who would otherwise experience unnecessary toxicity. It is perhaps especially important to collect tissue in these more rare positive trials which may alter the future standard of care and thus prevent forever the possibility of identifying those individuals who don't benefit.

In this lecture I will highlight some of the recent developments in basic science which are stimulating translational research in radiation oncology and discuss their implications on the ways to carry out effective clinical trials.

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Proteomics in translational cancer research

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The sequencing of the human and other important genomes is only the beginning of the quest to understand the functionality of cells, tissues and organs both in health and disease. Together with advances in bioinformatics, this development has paved the way to the revolution in biology and medicine that we are experiencing today. We are rapidly moving from the study of single molecules to the analysis of complex biological systems, and the current explosion of emerging technologies within proteomics and functional genomics promises to elicit major advances in medicine in the near future.

In particular, proteomic technologies are expected to play a key role in the study and treatment of cancer as they provide invaluable resources to define and characterize regulatory and functional networks, investigate the precise molecular defect in diseased tissues and biological fluids, and for developing specific reagents to precisely pinpoint a particular disease or stage of a disease. For drug discovery, proteomics assist with powerful tools for identifying new clinically relevant drug targets, and provide functional insight for drug development.

Today, the application of novel technologies from proteomics and functional genomics to the study of diseases is slowly shifting to the analysis of clinically relevant samples such as fresh biopsy specimens and fluids, as the ultimate aim of translational research is to bring basic discoveries closer to the bedside. Here I will describe our efforts to apply proteomics and functional genomic approaches to the study of fresh tissue and tumour biopsies as well as fluids obtained from breast cancer patients. The working strategy is based on the analysis of samples obtained from the same patient, which are rapidly distributed to various members of DCTB, who apply various experimental paradigms. Members of DCTB have access to the data through a centralised database.

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Oesophageal and gastric cancer – classification and surgical consequences

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As far as the upper gastro-intestinal tract is concerned, the TNM-classification is focused on prognosis rather than on the therapeutic consequences. From a therapeutic point of view, tumors of the upper gastro-intestinal tract have to be differentiated into squamous cell tumors of the esophagus, on the one hand, and stomach tumors, on the other.

Problematic is the classification of tumors located at the gastro-esophageal junction. Whereas the therapeutic consequences for squamous cell cancer of the esophagus (always sub-total esphagectomy) or for gastric cancer (always total gastrectomy) are no longer truly controversial, adenocancer of the gastro-esophageal junction still requires careful discussion. There is no conflict, however, about regarding this to be a single tumor entity. Internationally there is also agreement about further sub-classifying the entity in three types ("... we have defined and described adenocarcinomas of the esophagogastric junction (AEG) as tumors that arise within 5 cm proximal or distal to the anatomical cardia. We have differentiated three distinct tumor entities within this area." Br J Surg 85: 1457-1459,1998). Type I corresponds in most cases to distal Barrett cancer of the esophagus and type III can be categorised just as reliably as cancer of the stomach. Regarding the cancerogenesis and treatment of type II, however, (true cardia cancer), there are two hypotheses: one is that it originates as "short Barrett esophagus", and the other that it is in fact gastric cancer. Our own analysis of 100 prospective cases has revealed that in about 30% of cases goblet cells could be detected, thus providing support for the short Barrett hypothesis, but in 70% of cases the oncogenesis corresponded to that common in gastric cancer.

This classification has now found international acceptance and widespread usage and has led to greater precision in the discussion of therapeutic consequences and also enabled the recruitment of comparable patient populations in studies. There is considerable agreement that the treatment for type I is a sub-total esophagectomy and that types II and III both require an extended gastrectomy. The implementation of modern reconstruction techniques now makes proximal gastrectomies feasible and the discussion concentrates on comparing them with total gastrectomies.

Modern classification of tumors of the upper gastro-esophageal tract that incorporates therapeutic consequences has to differentiate between squa-