MONDAY 13 SEPTEMBER 1999

Teaching Lectures

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Cancer treatment – Major questions for the new millennium

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The way we treat cancer patients in the next twenty years will be radically altered by the explosion in genetic technology. To a certain extent the questions will depend on how fast that technology gets into the pathology laboratories of our various hospitals around Europe but my personal list is the following -

- Based on genetic information from an individual patient's cancer, is anti-metastatic treatment required?
- If systemic treatment is indicated by the genetic makeup of the cancer, should it be given before local treatment or before and after?
- Which drug should be used in which sequence based on the genetic resistance profile?
- If local treatment is required, should it be surgery or radiotherapy?
- If radiotherapy is required as the local treatment of choice, what dose should be given, based on genetic read-out? And is there a requirement for radio-sensitisation, be it with a DNA repair blocker, oxygen source or vascular interference?
- Is there a need for follow-up/maintenance therapy based on genetic instability of primary or secondary tumours?
- What is the chance of second malignancy and how can we predict it?

A great deal is going to be expected of the pathology laboratories and the genetic specialists who will have to be trained to provide the basic genetic read-out on which the above questions will rest. However, a genetic revolution will have much greater impact than merely in treatment, for instance in identification of high-risk populations and early diagnostic tests, these topics were dealt with elsewhere.

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Paediatric tumours – What have we learnt? General messages for oncologists

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Treatment of cancer in children and adolescents in the last 20–30 years has achieved remarkable progress. More than 70% of patients can be cured by modern strategies. There have been many important steps since the time when chances of survival were minimal to today's success. When considering this progress, several aspects should be mentioned: Cancer in childhood and adolescence is a rare disease with biological properties different from the majority of cancer forms in adulthood; remarkable progress was made in basic science allowing a better understanding of the diseases; this knowledge was tested through national and international clinical trials; therefore, for many years patients have been treated in highly specialised centres with interdisciplinary cooperation.

However, the dark side must be taken into account: Although we can cure 2/3 of paediatric cancer patients, the remaining third that we are still unable to cure with current strategies, remains the most difficult challenge for the future. Moreover, for families cancer is still traumatic, the diagnostic process is complicated, the therapy demanding and often life-threatening and the threat of relapse is constant! Also, the problems of long term sequelae are a matter of continuing concern.

By the year 2000, one person out of 900 in the population will be a long-term survivor of childhood cancer, many of whom will be suffering from late effects. Therefore, it is necessary to minimize this risk right now by tailoring treatment. Also, comprehensive follow-up care and supportive treatment, including social and psychological help need to be developed.

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The impact of biology on the practice of radiotherapy

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Radiotherapy is the oldest and most frequently used non-surgical treatment for cancer and originated from the work of Roentgen, a physicist, over 100 years ago. Many major advances in RT, for example, megavoltage machines, computerised planning systems, stereotactic localisation and electron beam therapy, have been driven by the physics community not by biological research. The biggest biological contribution to radiotherapy is undoubtably fractionation around 70 years ago and the science of radiobiology has remained somewhat fixated on this area and its underlying dogma of the "4 Rs" of repair, repopulation, reoxygenation and reassortment. This has given rise to thais of therapies such as hyperbaric oxygen, radiosensitisers and more recently altered fractionation schedules such as CHART, probably the only therapeutically useful insight generated since fractionation by 70 years of mainstream radiobiology.

Most non-surgical cancer therapies are given in combinations, based on the insights of Goldie and Coldman on probability of drug resistance and cure, rather than at the maximal tolerated dose of a single agent. The use of drug combinations has resulted in striking advances such as CHOP for lymphoma and BEP for testicular tumours. Belatedly, combinations of radiotherapy with other anticancer therapies are now being actively explored and are resulting in striking improvements across a wide range of disease types, good examples being cancers of the anus and cervix. The potential interactions are complex and should result in cross-talk between the often relatively isolated radiobiology community and more mainstream drug development, which should yield new therapeutic opportunities. A further area of biological contribution to radiotherapy is in targeted therapy, for example, radioimmunotherapy; metabolically targeted treatments, from 131I to 89Sr and more recently boron neutron capture therapy. Other areas under investigation, but not yet impacting on clinical practice include prediction of radiosensitivity and gene therapy using radiosensitive promoters. The future impact of biology on radiotherapy is likely to grow and may help to move the field away from the hardware driven, dose escalation model that has dominated much of the last 50 years but which is inherently limited by biological diversity and in particular metastatic disease.

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Vascular endothelial growth factors and receptors involved in angiogenesis and lymphangiogenesis

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Angiogenesis, the formation of new blood vessels from preexisting ones, and the permeability of blood vessels are regulated by vascular endothelial growth factor (VEGF) via its two known receptors Flt1 (VEGFR-1) and KDR/Flk-1 (VEGFR-2). The Flt4 receptor tyrosine kinase is related to the VEGF receptors, but does not bind VEGF and its expression becomes restricted mainly to lymphatic endothelia during development. Homozygous Flt4 knock-outs die after E9.5–10 due to failure of cardiovascular development. We have purified the Flt4 ligand, VEGF-C, and cloned its cDNA. While VEGF-C is homologous with other members of the VEGF/platelet derived growth factor family, it is made as a precursor protein having an extended N-terminus and a C-terminal half containing extra cysteine-rich motifs characteristic of a protein component of silk. VEGF-C is proteolytically processed, and binds and activates Flt4, which we rename as VEGFR-3. Transgenic mice expressing VEGF-C under a basal keratin promoter developed a hyperplastic lymphatic vessel network in the skin. However, proteolytically processed VEGF-C was also capable of stimulating VEGFR-2 and was weakly angiogenic. VEGF-C also induced vascular permeability, but its point mutant, which activated only VEGFR-3 did not. VEGF-D is closely related to VEGF-C, proteolytically processed and binds to the same re-