Teaching Lectures

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Basal, squamous, Merkel cell carcinoma

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Diagnosis: after a careful history the diagnosis of malignant skin lesion is essentially based on the clinical presentation; this clinical presentation varies for basal cell ca (BCC), squamous cell ca (SCC) and Merkel cell ca (MCC) also called cutaneous neuro-endocrine carcinoma. To illustrate different tumoral aspects many slides will be shown.
Management: for skin carcinoma (excluding malignant melanoma) there is no consensus in the literature concerning the respective role of surgery and radiation therapy. For each therapeutical approach indications and techniques are described from electro-coagulation to chemotherapy going through cryotherapy, surgery, radiation therapy (external beam irradiation, brachytherapy), chemotherapy. The treatment takes into account the pathology but also tumor size and site.
Results: BCC and SCC represent more than 90% skin malignant tumors. MCC was individualized about 30 years ago and represent less than 2% of them. The reported overall survival and local control rate at 5 years are respectively 95% and 80% for BCC, 90% and 75% for SCC, from 75 to 60% and from 68% to 30% for MCC.
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How to conduct clinical studies form phase I-III

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In oncology, clinical trials are largely used to define new treatment tools and validate them in clinical practice. The rules to make relevant trials are widely known : review the existing scientific data, ask a good question, define the target population, quantify the number of patients to be included, conduct the study in an ethical way, evaluate the results and publish (whatever is) the result. All these parameters are largely defined as « good clinical practice » and follow some written guidelines. Conducted by individuals or co-operative groups, they are before hand submitted to ethical committees and regulatory bodies dedicated to assess the relevance of the study proposed and its accordance to international and national regulations and laws on research in human beings. However, all these basic principles may not be always followed. Most of phase I and II studies are promoted and sponsored by groups not totally dedicated to the advancement of science and negative results or observed toxicities are not very often fully reported. They are not reported not only because they are not submitted to peer reviewing process but because they are not considered by reviewers as scientifically worthwhile publishing and this is equally true for negative phase III studies. Anyone should consider that any clinical study on patients should be reported in a way or another after its completion and be available to the scientific community (dedicated web sites ?). Due to the lack of transparency observed, the most important danger for future clinical studies is linked to the patients themselves. When a cancer patient comes to have a clinical advice, he (she) requires to get the best available treatment at the time from the physician. Even if some highly relevant interrogations remain, to allocate a treatment by random is, and will be, more and more difficult to justify. In parallel to the very justify need to have scientific answers, it will be crucial for clinical researchers and statisticians to define new ways of comparing different treatment on different patients that by randomisation alone.

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Molecular mechanisms of cellular radiation responses

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Ionizing radiation (IR) interacts with cells through indiscriminate activation of multiple existing cellular signal transduction pathways in different cellular compartments. Response measurements after irradiation identify DNA damage recognition and membrane receptor activation as the earliest measurable events that are followed by complex responses involving oncogenes and cytoplasmic protein kinases as signal modifiers and transducers. These signals are converted into changes of transcription, cell cycle checkpoint control and overall cellular responses of survival or death by apoptotic or other mechanisms; thus, IR induces both cytotoxic and cytoprotective responses.
The pro-survival cyto-protective responses are likely initiated by immediate activation of receptors in the membrane. Similar to effects of growth factors, the signal by ERBB1 (EGFR) is transmitted through the RAS, RAF, MEK1/2, MAPK cascade with parallel signals generated, through ERBB3, along the PI3K pathway. MAPK and PI3K stimulate transcription through P90S6K and P70S6K, respectively, ultimately leading to a proliferation response. The activation of AKT through ERBB2/-3 (and IGF-1R/SRC) leads to STAT3-dependent over-expression of anti-apoptotic BCL protein(s) and mediates an anti-apoptotic response that contributes to the overall cytoprotective response.
Cytotoxic responses are mediated by the RHO/RAC1/RAS, MEKK1-3 pathway that signals to activate MAPKK4/7 (by MEKK1) and JNK which in turn phosphorylates c-JUN promoting apoptosis in certain cells. JNK may also exert a cytoprotective response, similar to MAPKK3/6, that activates P38 of a rescue pathway resulting in increased cell survival. Besides RAS, ceramide can shift the balance between the MAPK and JNK pathways. Other consequences of JNK activation include induction of cytokines, such as FAS-1 and TNF-a, which activate death receptors with secondary cleavage of effector caspases and induction of apoptosis.
IR-induced signaling is also generated by DNA damage recognition and repair which are tightly linked to altered cell cycle regulation and may also depend on receptor expression and the functions of stress and cytoprotective kinases.

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NTCP in the clinic

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NTCP (Normal Tissue Complication Probability) models describe the probability of complication induced by radiotherapy to normal tissue.

The clinical implications of this type of modelling can be far reaching. A knowledge of the dose-response relationship characterizing a specific tumor and specific complications will allow to quantify the probability of benefit and injury in classical dose planning. Furthermore dose-response relationship is used as biological objective function in optimization algorithms.
As in all cases of modelling, NTCP modelling is based on some hypotheses which, whether correct or not, have to be respected while applying it. Several models have been proposed; however, the overall uncertainties in the data sets and in the modelling procedures themselves are still quite large.
NTCP and TCP (Tumor Control Probability) tools are now offered by several treatment planning systems; user-friendly software for TCP and NTCP calculations has also been prepared and it is spreading in more centers. However, up to now in very few cases NTCP has been incorporated in the clinical practice; the lack of an extended validation of the modelling (both formalism and data) seems to be one of the main reasons for the delay of the process. In most centers the dose planning choice is based on the evaluation of the physical dose distribution, sometimes accompanied by the observation of the DVHs and, in some cases, on the respect of dose-volume constraints criteria.
In some centers, however, NTCP calculations have been introduced in the clinic, both in the routine, where NTCP values or indirect measures of them are used as further criteria in the dose planning choice and in the development of new treatment techniques, and in dose escalation studies. The specific case of the use of NTCP models for rectum, liver, brain, lung and heart will be described.

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Drug prescribing and treatment review by therapy radiographers - for and against

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The role extension of therapy radiographers to encompass the ability to prescribe drugs to relieve or prevent the acute side effects of radiotherapy is considered. Therapy radiographers are enthusiastic to extend their roles in this way, but is this practice in the best interests of patients?
The patients need to be sure that the drugs they receive adhere to evidence based protocols and that they continue to receive care in a timely fashion. Radiographers leaving the Linacs to undertake this role should not compromise the daily throughput of patients for treatment.
Bristol Haematology and Oncology Centre has 10 radiographers trained and undertaking this role. Evaluation of this role has considered the type of patients involved as well as the extent of the symptom care provided, in addition to the quality issues for patients.
Preliminary data from our Centre suggests that 80% of patients receiving this care from radiographers were receiving radical rather than palliative radiotherapy. 78% of patients reviewed by radiographers received advice and medication, 8% received advice only and 14% were referred for a medical opinion. A small retrospective study confirmed 100% adherence to protocol and that the time taken by radiographers to deliver care directly did not appear to exceed the time taken for radiographers to access conventional care by medical staff.
Corresponding results from the completed evaluation will be presented and their relevance to future care by therapy radiographers discussed.