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Management of quality of life after cancer treatment: what place in daily practice?

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The long-term survival rate has improved considerably in many cancer types over the past decades due to advances in early detection and multidisciplinary treatment.
Therefore, the number of people suffering from long-term toxicity due to anti-cancer treatment also increases and issues of quality-of-life after treatment are becoming more and more important. Long-term side effects may be due to loss of function (surgery, radiotherapy) or toxicity to tissues (radiotherapy, medical treatment).
They should be monitored in daily clinical practice and evaluation tools commonly used to evaluate acute side effects by anti-cancer treatment have been expanded to long-term side effects (e.g. RTOG/EORTC late radiation morbidity scoring scheme) and new tools (e.g. Minneapolis-Manchester Quality of Life Instrument) have been developed and validated.
It is important to limit or prevent the development of these long-term side effects already during treatment. This may be done by specific surgical intervention (e.g. organ-sparing surgery), radiation techniques (e.g. limiting radiation fields; intensity-modulated radiation therapy) and use of specific medical treatment schedules or cytoprotective agents.
If long-term side effects are present, they may be reversed (reconstructive surgery) or alleviated by specific treatments.
Not only long-term physical toxicity should be considered but also the psychological and social impact of a previous anti-cancer treatment should be taken into account in daily clinical practice.

Scientific Symposium
Developments in molecular imaging

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Molecular imaging with oligonucleotides

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Characterization of gene expression anomalies in tumour samples has advanced considerably our understanding of cancer, and paved the way to the identification of new molecular targets for therapy and diagnosis.
Molecular Imaging is presently building a remarkable tool box which will allow assessing gene expression non–invasively, repeatedly and quantitatively in living subjects. For that purpose, oligonucleotides are one of the major bio-molecules under development.
Molecular imaging with oligonucleotides has two principle objectives:

1. Pharmaco-Imaging of oligonucleotides designed as **drugs** for therapy of cancer. These include antisense, aptamers and – in the future – interfering RNAs, ribozymes, ribo switches, etc. In this context, the power of imaging techniques such as Positron Emission Tomography (PET) offers a unique opportunity to quantify in 3-D and in the whole body of animals and Humans the time course of the bio-distribution of new drug candidates. The accuracy of PET is such that the pharmaco-images produced can be directly used for cancer drug development.
2. Development of oligonucleotides as **targeting** agents for the molecular typing of tumours *in vivo*. This objective is more difficult and will take more time to reach, because of the necessity to obtain a sufficient contrast (i.e. signal to noise ratio) and to demonstrate the correlation between tracer and target concentrations. Aptamers are presently the most promising oligonucleotides in that respect, especially those targeting extra cellular proteins which facilitate systemic access of the tracer, while antisense imaging is more challenging due to the necessity to target the intra cellular compartment in which the mRNAs are located.

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Molecular imaging as possible clinical tool

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The lecture will discuss the potential role of biological imaging in predicting and monitoring response to therapeutic interventions in cancer. Response evaluation based on morphologic criteria is limited due to lack of specificity for malignant tissue. Change of tumor size assessed by CT is commonly applied as marker of clinical response, but has limited predictive value for clinical outcome. In lymphoma patients comparison of metabolic imaging after therapy with CT assessment of tumor volume demonstrated a higher predictive value of FDG-PET for progress free survival. Several studies in lymphoma and solid tumors support the notion that metabolic imaging with F-18 deoxyglucose (FDG) delineates accurately residual tumor viability of treated patients. F-18 FDG uptake decreases rapidly within 1–2 weeks after initiation of therapy. Studies in pts with esophageal cancer undergoing a neoadjuvant regimen have shown that the early decrease of FDG uptake of more than 35% is highly predictive of response assessed by histology and is associated with significant longer survival. Therefore, non-responding patients based on PET may be withdrawn from therapy; a strategy currently tested in the Municon trial. Use of radiolabelled amino acids such as C-11 methionine are less predictive for therapy response as compared to FDG in pts with colorectal cancer. Amino acid transport rates decrease rapidly in responding and non-responding patients. These results suggest high sensitivity of amino acid transport to cytotoxic interventions, but a lack of specificity for tumor cell kill.
Newer tracer approaches including markers of hypoxia or angiogenesis may provide individual visualization of tumor biology and guide interventions such as radiotherapy. F-18 misonidazole and F-18 FAZA are retained in hypoxic tumor areas providing high imaging contrast for the delineation of the hypoxic tumor fraction.
Identification of target structures for molecular therapies by PET imaging may be attractive for optimized patient selection. $\alpha_v\beta_3$ integrines expression can be monitored by PET using RGD peptides guiding therapeutic strategies, which block integrine interaction with endothelial as well as tumor cells. It is anticipated, that therapy targets may not only be identified prior therapy, but also be probed during therapy in order to examine target occupancy by a given drug. Combining molecular with anatomic imaging as possible with PET/CT will improve quantification of biological signals. However, the comparison of molecular imaging with clinical outcome needs to be addressed by prospective PET studies in order to define the value of surrogate endpoints. Such endpoints are expected to assist in the validation of new drugs and will accelerate drug development process.

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Molecular imaging for oncology drug development

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Molecular imaging uses quantitative functional imaging technology to look at molecular pathways *in vivo* in man. It is emerging as important to the development of anti-cancer therapies. Positron emission tomography (PET) is the most sensitive and specific technique for imaging molecular pathways *in vivo* in humans. PET uses positron emitting radionuclides to label molecules, which can then be imaged *in vivo* in humans. The inherent sensitivity and specificity of PET is the major strength of this technique. PET can image molecular interactions and pathways, providing quantitative kinetic information down to sub-picomolar levels.
Molecular imaging can provide pharmacokinetic, pharmacodynamic and mechanistic information. Use of the technique in early drug development studies provide information on optimum biological dose and PK/PD relationships, identify tumours containing specific molecular targets and provide *in vivo* pharmacodynamic evaluation of compounds. Its use can also investigate *in vivo* pharmacokinetics. Molecular imaging provides information *in vivo* in humans as to whether the drug is hitting the target, the target is expressed in an accessible way, what are the timing and magnitude of such molecular interactions and if the molecular interactions have the desired downstream effect.
Advantages of knowing this information early *in vivo* in humans can speed up drug development, stop compounds early if they prove not to have the desired mechanism, be used for *in vivo* target validation and for identification of new targets. As anti-cancer strategies become more directed towards a defined molecular target, we need information that is relevant to humans about whether the molecular target is expressed, the selectivity and binding of the compound for that target, and the effects of such an interaction.
With new regulations in place, microdosing PET studies should be easier to undertake for first into man compounds. There is a growing acceptance in the drug industry that markets need to be segmented. PET is an ideal tool for developing biomarkers in this field. This could lead to the more rapid development of successful anti-cancer compounds.

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MR spectroscopy in cancer research and diagnosis

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MR spectroscopy (MRS) of living intact animals or humans provides a window on the presence and tissue levels of a number of metabolites and drugs, which are relevant in cancer research and diagnosis.