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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

62 INVITED

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.

63 INVITED

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.

64 INVITED

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.

65 INVITED

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.

The resonance that can be observed arise from natural stable isotopes in these compounds, mostly those of ^{1}H, ^{31}P, ^{19}F and ^{13}C. Because of some limitations inherent to the MR technique such as sensitivity, the use of MRS in vivo usually is restricted to a set of small metabolites, which are present at tissue levels of more than about 0.1 mM. These are metabolites that play important roles in energy metabolism (e.g., ATP, lactate) and in lipid metabolism (e.g., choline compounds, triglycerides). Furthermore, as resonance frequencies are also sensitive to physiological environment of the metabolites other parameters such as tissue pH can be determined by MRS. The nucleus of ^{19}F mostly has been used to monitor metabolism of drugs like 5FU and the nucleus of ^{13}C to follow metabolic fluxes as ^{13}C can be applied as a non-ionising label due to its low natural abundance.
The non-invasive nature of MR allows one to perform longitudinal metabolic and physiological examinations.
These properties of in vivo MRS have been exploited in numerous experimental studies in oncology.
Often in these studies the MRS investigations are combined with other information that can be obtained (simultaneously) by different MR approaches such as on blood flow or oxygenation. MR spectroscopy has also been applied to tissue biopsies or extracts of whole tumours or tumour cells, by which higher sensitivity and better spectral resolution can be achieved. The research that records and exploits metabolic profiles of tissues or cells by MRS or otherwise sometimes is referred to as metabolomics.
The use of MRS in cancer diagnosis is largely restricted to the use of the ^{1}H nucleus. This is the most sensitive nucleus (allowing the measurement of relatively small volumes and therefore the registration of tumour heterogeneity) and can be easily combined with (routine) clinical MRI approaches, which are based on the observation of the ^{1}H nucleus in body water. Although MRI is often able to record lesions that may represent tumour tissue it is generally difficult to make a differential diagnosis with respect to pathologies that cause similar types of lesions. As MRS may provide metabolic information that is more specific its use in tumour diagnosis was attempted already some time ago. Only in the last 5 years the technology of human MRS has evolved to such a level that this became possible in a clinical environment. The most important cancers in which MRS is now being used for diagnosis, grading and treatment evaluation are brain, prostate and breast tumours.
New developments in which MRS methods are involved that could be applied to tumour research and diagnosis, include the emerging field of molecular imaging combining different imaging modalities (although MRS can be considered as molecular imaging avant la lettre) and the use of hyperpolarisation to boost the sensitivity of MRS.

Scientific Symposium
Colorectal cancer can be prevented

66 INVITED

Colorectal cancer can be prevented: epidemiology and primary prevention

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Colorectal cancer is the second most common incident form of cancer in Europe and also the second most common cause of cancer death. Comparison of incidence and mortality rates over long periods of time clearly demonstrates that the mortality rates are declining at the same time as the incidence is rising. In the European Union, colorectal cancer mortality is fifty percent higher in men than in women and the mortality rate is higher in men than in women in each Member State of the European Union. The highest national mortality rates recorded in men are in Ireland, Denmark, Austria, Luxembourg and Germany. The lowest rates are recorded in Greece, Finland, Iceland and Sweden. The pattern is quite similar in women.
Colorectal cancer is clearly an important and increasing Public Health concern although there is room for optimism with respect to the possibility that prospects for the prevention of colorectal cancer could be found. It is clear that there are dietary components which can modify an individual's risk of colorectal cancer as can related lifestyle issues such as physical activity and overweight. While it is possible to be optimistic, there is still more research needed to identify the precise dietary components associated with colorectal cancer risk. When this is clarified, prospects for prevention will greatly improve although a balanced diet, rich in fruits and vegetables and fibre, with a general tendency for more fish and chicken rather than red and processed meat, accompanied by a sensible physical activity programme and achieving stability of body weight (for height), will almost certainly reduce the risk of colorectal cancer as well as of other chronic conditions.
The declines in the mortality rates from colorectal cancer in many (developed) countries in the presence of increasing incidence, represents a great advance in cancer control. This probably represents a success for increased awareness and (probably) subsequent stage drift over time; although there have been treatment advances these have mainly led to the most appropriate treatment being given to the most appropriate patient. However, successful primary prevention looks an attractive possibility in the not-so-distant future.

67 INVITED

Secondary prevention and screening for colorectal cancer (CRC) in the average risk population

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There are several options for CRC screening. Fecal occult blood testing (FOBT), by Haemoccult, is the most extensively examined method. This home-test kit requires collection of two samples from three consecutive stools, which are smeared onto cards and mailed to a laboratory for processing. Colonoscopy is recommended if any of the cards are positive since up to 50% will have a cancer or large adenoma. Biennial FOBT has been shown, in three randomised trials to reduce CRC mortality by a 15–20%. Immunochemical tests for haemoglobin or other blood components show greater sensitivity for both CRC and adenomas but at the expense of lower specificity. Flexible sigmoidoscopy (FS) is sensitive for the detection of distal adenomas. Three randomised trials are in progress. The protection afforded by a single FS may last for up to 10 years or even longer depending on the age at which it is undertaken. Two trials are examining the efficacy of a single FS at age 55–64. Colonoscopy screening at 10-yearly intervals from age 50 years is now considered the gold-standard test in the US. However data on the efficacy of colonoscopy in reducing proximal colon cancer rates and on the feasibility of offering 10-yearly high-quality, safe colonoscopy are lacking Potential future methods include examination of molecular markers in stool, and MRI and CT colonography, which are safer and better tolerated than colonoscopy. The sensitivity of both techniques for CRC and large adenomas seems high, although results vary by centre with a steep learning curve. If accuracy improves, costs reduced and the need for bowel-preparation eliminated, there may be a role in average-risk screening.

68 INVITED

Hereditary and familial colon cancer syndromes

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Although most colorectal cancers occur sporadically, about 25% arise in a familial context and 5 to 7% percent have an autosomal dominant inheritance and occur in genetically distinct high risk families. Colorectal cancers, whether sporadic or hereditary, are caused by a defined set of molecular events.
There are at least two different pathogenetic pathways for colorectal cancer: the chromosomal instability pathway and the microsatellite instability pathway; the two major inherited syndromes, familial adenomatous polyposis (FAP) and Hereditary non-polyposis colorectal cancer (HNPCC) are caused by germline defects in these pathways. These different pathways, however, converge on common pathological entities that have crucial functions in the regulation of normal crypt homeostasis. Further insight into colorectal tumorigenesis pathways can lead tot the development of useful prognostic indicators and target preventive and therapeutic strategies in the management of colorectal cancer.
Advances in the management of hereditary colorectal cancer syndromes have been principally due to advances in the understanding of the genetics of these syndromes. This has led to the possibility of preclinical genetic diagnosis and early surveillance and prevention strategies. In addition, improvement in medical and surgical management have also occurred. However, risk stratification is essential to the appropriate use of colorectal and extraintestinal cancer screening methods. Effective educational strategies that promote physician awareness regarding familial risk, risk assessment skills, and appropriate use of relevant screening guidelines are needed. Nevertheless, various vexing problems can deter the diagnosis and management of these syndromes, such as lack of medical and pathological documentation, poor cooperation of family members and/or their physicians, cultural barriers, economic issues, patient fear and anxiety.
This presentation will provide a overview of the hereditary and familial GI cancer syndromes, aiming to help clinicians in the recognition and management of this disorder. This can be a challenge, for instance the rapid advances in molecular medicine can be difficult to integrate in clinical practice. Hence we will also emphasize issues such as when and how to