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Future trends in the management of epithelial ovarian cancer

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Only new trends in early detection and more adequate evaluation of prognostic factors will be able to change, in the future, the bad course of epithelial ovarian cancer.

In our opinion recent advances of knowledge on molecular structure and genetic changes of neoplastic cell phenotype and on many new prognostic factors concerning the mechanisms of ovarian carcinogenesis will be able to predict cancer evaluation and its response to different treatments.

In the future it will also be possible to better modulate surgery and chemotherapy on the basis of well known and new prognostic factors, like surgical pathologic stage, histological types and grading (new grading evaluation combines architectural features, nuclear grade and mitotic count) P53 tumor suppressor gene, apoptosis, drug resistance markers, hereditary and immunologic conditions, steroid hormone receptors, tumor angiogenesis, molecular biologic markers and cromosomal abnormalities (cromosomal aberrations, loss of heterozygosity).

If further research will confirm their value, a reliable identification of low and high risk patients will allow to avoid inadequate or unnecessary therapies in a personalized management.

These fascinating new perspectives will be broadly examinated.

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Nuclear medicine: The functional approach to oncology

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The role of nuclear medicine in oncology is expanding and changing, particularly in tumour imaging, function analysis and radionuclide therapy.

Techniques have changed from analogue spot views to digital whole body imaging, showing tumours and metastases regardless of their localisation in a single procedure. Single photon emission tomography (SPECT) and positron emission tomography (PET) allow 3-dimensional display.

Tumour Imaging: a great number of highly specific tumour-seeking agents are available, exploiting a variety of metabolic and biological properties of tumours. Where radiological techniques aim at anatomical delineation of the tumour, nuclear medicine utilizes its functional characteristics. The focus of interest is shifting from tumour detection to tumour characterisation. Radionuclide tumour imaging may also be helpful in the monitoring and early prediction of response, as changes in the tumour's function often proceed anatomical response. For sentinel node biopsy in melanoma, breast carcinoma and penile cancer the lymphatic drainage pathways and sentinel nodes are detected by lymphoscintigraphy, identified with the probe and selectively resected.

Monitoring of Organ Function: as a functional modality nuclear medicine is highly suited for the monitoring of organ function which is at risk during oncological therapy. Many techniques are available to document side effects and study the effect of interventions to prevent or treat toxicity.

Radionuclide Therapy: this treatment modality is characterised by selective delivery of radiation doses to tumours, combining the advantage of being selective like brachytherapy with that of being systemic like chemotherapy. Its limited immediate and longterm side effects compare favorably with those of chemotherapy and external beam therapy.

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Position emission tomography (PET) for in vivo pharmacokinetic & pharmacodynamic assessment of anticancer therapy

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PET is the most sensitive and specific means for studying, through imaging, molecular interactions in man. The kinetic behaviour of tracers labelled with short-lived cyclotron produced positron emitting radionuclides can be studied *in vivo*. The CRC Phase I/II Drug Development Committee are, with the MRC Cyclotron Unit, developing PET methodology to study *in vivo* tumour and normal tissue pharmacokinetics and pharmacodynamics.

PET can look at such pharmacodynamic endpoints as changes in tumour perfusion and blood volume in response to anti-vascular and anti-angiogenic therapy, changes in thymidine retention as a surrogate marker for changes in DNA synthesis in response to anti- proliferative agents. Future developments will be able to quantify the degree of hypoxia in tumours and their change with therapy as well as looking at mechanisms of resistance.

Up to 50% of anti-cancer drugs can now be theoretically labelled with positron emitting tracers. With this we are able to look at the *in vivo* pharmacokinetics in normal tissues and tumours. This can be used prior to Phase I or paralleling Phase I/II studies. The *in vivo* mechanism of action of anti-cancer drugs can also be studied in this way.

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MRS and MRI techniques in cancer

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Magnetic Resonance Imaging (MRI), like MR Spectroscopy (MRS), is fundamentally non-invasive; it is already the method of choice for much routine cancer diagnosis and monitoring. A recent development is FLOOD (FLOw and Oxygen Dependent) MRI, which detects changes in blood flow and deoxy-haemoglobin content of tumours in response to challenges such as carbogen breathing.

MRS, which is beginning to come into routine use, has the unique ability to monitor body chemistry (and pH) continuously and noninvasively, although unfortunately its sensitivity is quite low. Drug pharmacokinetics and pharmacodynamics can be monitored, however, as well as response to radiotherapy. We have combined FLOOD MRI and ^{19}F or ^{31}P MRS detection of 5FU and ifosfamide to show that carbogen breathing can enhance drug uptake by tumours. Response of tumours in many parts of the body can be monitored by ^{31}P MRS, since the peak due to phosphomonoester compounds decreases rapidly when therapy is successful. Brain tumours are easily monitored by ^{1}H MRS, and we and others have developed automated, objective computer programmes that can diagnose and grade them with reasonable (ca80%) accuracy.

Using ^{19}F MRS we can monitor the metabolism of fluoro-deoxyglucose to FD-mannose in mouse RIF-1 tumours. FD-mannose formation predicts response to therapy with 5FU better than FDG uptake.

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Fast dynamic contrast MRI

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Fast dynamic contrast enhanced MRI (dMRI) provides both semi-quantitative and quantitative data on tumour angiogenesis. Semi-quantitative studies rely on analysis of signal intensity-time curves, whereas quantitative analysis requires calculation of contrast agent concentration with time using pharmacokinetic modelling techniques. Quantification analysis has the advantage of permitting absolute values of capillary permeability and extracellular leakage space. These measurements are based on T1 weighted imaging. Recently T2* weighted imaging techniques have been developed which provide information on tissue perfusion, characteristics. Recent clinical studies indicate that dMRI is a valuable tool for tissue characterisation, tumour staging, and monitoring therapeutic response.

The different techniques of dMRI will be discussed focusing on bladder and prostate cancer. The role of dMRI in the clinical management of prostate cancer will also be addressed.

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Radio frequency percutaneous liver tumour ablation

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Percutaneous radio-frequency liver tumour ablation (RFA) was first reported in 1993. It is performed with a small 17G needle connected to a generator that produces current with a frequency between 450 and 500 kHz. The heating is generated by the electric field that induce molecular friction in the tissue surrounding the needle tip. RFA can be performed on an outpatient basis.

Ultrasound is the modality of choice of guidance since real-time imaging is possible, as is angulation of the access tract. Recent developments of MR, including real-time, open units, non-ferromagnetic needles and accurate thermal map for monitoring induced lesions, hold promise for multiplanar guidance.

RFA is used in 2 different ways: conventional percutaneous image-guided ablation, and as an adjunct to hepatic resection during open surgery to allow

complete tumor ablation in patients who could not have been cured with conventional surgical techniques.

Vessels walls are protected from over-heating by the intra-luminal blood flow that induces thermal dispersion, so that even lesions developping in the very vicinity of large vessels can be treated. No major complications have been reported with this technique. Results in the literature and personal datas will be reported and discussed. Special attention will be paid to imaging follow-up of the treated patients, for whom standard morphological analysis is not relevant.

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MR-guided percutaneous vacuum biopsy of breast lesions: Experiences with 100 cases

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Based on its excellent sensitivity MRI is able to contribute valuable additional informations for appropriate indications (posttherapeutic breast, preoperative patients, high risk patients). However, only part of the MR-dedected lesions prove to be malignant. So far MR-guided open surgery after MR-localisation and MR-guided needle biopsy are difficult procedures. By combining a new "breast biopsy coil" with a vacuum biopsy needle we have been able to percutaneously excise enhancing areas of up to 1.5 cm diameter based on MR-guidance. So far 99/100 procedures (performed under local anaesthesia) have been successful yielding malignancy in 25% of the cases and a definitive benign diagnosis in 75%. The procedure was well tolerated and proved very accurate as proven by reexcision of malignant lesions and MR-follow-up of benign lesions.

Value and future possibilities of this new method will be discussed.

Patentholder: S.H. Heywang-Köbrunner

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A TRAIL towards tumour therapy

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TNF Related Apoptosis Inducing Ligand (TRAIL) is a type II transmembrane protein that is capable of inducing apoptosis in a wide variety of transformed cell lines, but not normal cells, in vitro. A leucine zipper form of recombinant human TRAIL (LZ-huTRAIL) was created to promote and stabilize trimerization of this molecule, and purified recombinant LZ-huTRAIL was demonstrated to have potent biological activity in vitro. Extensive testing of human tumors to the cytotoxic effects of LZ-huTRAIL has shown that 57 of the 77 cell lines tested are sensitive to the cytotoxic effects of LZ-huTRAIL. Interestingly, although LZ-huTRAIL is potently cytotoxic to a wide range of human tumor cell lines, it is not toxic to normal human tissues in vitro, and failed to induce any detectable toxic effects in mice. To determine the potential therapeutic potential of LZ-huTRAIL in vivo a mouse xenograft model was established using the MDA-231 human breast adenocarcanoma in CB.17 SCID mice. The therapeutic potential of this molecule was demonstrated by the fact that repeated injections of LZ-huTRAIL not only suppressed growth of MDA-231 tumors, but also caused complete remission in a high proportion of the test subjects. In addition, the therapeutic potential of LZ-huTRAIL can be potentiated when used in combination with chemotherapeutic agents. Histologic examination of tumors from LZ-huTRAIL-treated SCID mice demonstrated clear areas of apoptois within 9–12 hours of injection, but manifest no apparent toxicities to normal tissues. These results indicate that TRAIL may have a substantial potential in therapy of human cancers.

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The role of mitochondria in apoptosis

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In response to most pro-apoptotic signal transduction pathways or lethal damage pathways, mitochondrial membrane permeability is compromised, leading to the disruption of essential mitochondrial functions and/or the selective release of soluble mitochondrial intermembrane (not matrix) proteins (SIMPs). Several among these SIMPs have potential apoptogenic properties: apoptosis inducing factor (AIF), because it can translocate to the nucleus where it causes chromatin condensation and large scale (50 kBp) DNA fragmentation; pro-caspases 2, 3, and 9 because they participate in the caspase activation cascade; and cytochrome c because it interacts with Apaf-1 to activate caspase-9. If these proteins, in particular caspases, become activated, they give rise to typical apoptotic cell death. In contrast, when caspases are inhibited (or when their activation is prevented due to the depletion of the Apaf-1 co-factor ATP), cells die from a bioenergetic catastrophe without acquiring the apoptotic morphology. What determines cell death thus is not always the action of SIMPs. Rather, cell death is determined by the underlying cause of SIMP release: mitochondrial membrane permeabilization. It appears that both anti-apoptotic Bcl-2-like proteins and proapoptotic Bax-like proteins act on mitochondria to inhibit or favor membrane permeabilization, respectively. These effects are, at least in part, mediated via interaction with sessile mitochondrial proteins from the permeability transition pore complex (PTPC). This scenario has important implications for the understanding of pathology-related dysregulations in apoptosis, as well as for the design of therapeutic strategies aimed at correcting such imbalances.

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Caspases and apoptosis

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Caspases are a family of aspartate specific cysteine proteases which contain an N-terminal peptide (prodomain), together with one large and one small subunit. Activation of caspases during apoptosis results in the cleavage of a wide array of cellular substrates which precipitates the dramatic morphological, and biochemical changes associated with apoptosis. Caspases can be divided into the "initiator" caspases (those caspases with long prodomains) and "effector" caspases (with short prodomains), such as caspases-3, -6 and -7. Caspase-8 is the most apical caspase in cell death receptor (CD95, TNF or TRAIL) induced apoptosis. Procaspase-9 is the most apical caspase in a post-mitochondrial caspase cascade. Procaspase-9 is activated following interaction with Apaf-1 in the presence of ATP/dATP and cytochrome c. We have now isolated an ~700 kDa caspase activating complex which contains Apaf-1, activated caspases -3, -9 and -7. Recently we have also shown that proteasome inhibitors induce apoptosis in B chronic lymphocytic leukaemia (B-CLL) cells and proteasome inhibitors result in the processing of caspases-3, -7, -8 and -9 prior to the activation of caspase-2. We propose that the proteasome inhibitors induce apoptosis in B-CLL cells by initiating a caspase cascade with caspase-9 as the "initiator" caspase. Thus, the defect in apoptosis in B-CLL cells appears to be in the signalling which regulates caspase activation, as the cells possess all the requisite caspases required for execution of the apoptotic program.

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Lipid mediators of apoptosis

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Cross-linking off surface "death" receptors induces apoptotic cell death in a variety of cell types. Two main biochemical pathways originate from receptors "death domain" to propagate the early apoptotic signals. A proteolytic cascade initiated by caspases, and sequential activation of phosphatidylcholine-specific phospholipase C (PC-PLC) and acidic sphingomyelinase (ASM), which results in ceramide accumulation. ASM-derived ceramide is then rapidly utilized for the neosynthesis of gangliosides. The transient accumulation of GD3 ganglioside, synthesized by the action of a2,8-sialyltranferase (ST8), is crucial for early recruitment of mitochondria to the apoptotic program. In fact, GD3 directly reduces loss of mitochondrial transmebrane potential, mitochondrial swelling, and release of reactive oxygen species and apoptogenic factors, including cytochrome c ad AIF. Genetic abrogation of the lipid pathway significantly prevents cell death. Therefore the PC-PLC/ASM/ST8 lipid pathway cooperates to the apoptotic program by contributing to the early mitochondrial damage.

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CD95, apoptosis pathways and cancer therapy

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Homeostasis in tissues is tightly regulated by cellular programs which control proliferation or apoptosis. Apoptosis may be induced by cellular receptors