The overall survival for patients with malignant carcinoids tumors and the carcinoid syndrome has increased for the last two decades from medium two years to more than nine years today. Improved diagnosis and treatment are the best explanation for this improvement.

In the future new therapies will emerge mostly based on current tumor biology including tyrosin kinase and angiogenesis inhibitors. New somatostatin analogues (som 230) are also in the pipeline for testing in neuroendocrine tumors and further development of tumor targeted radioactive treatment is ongoing. Vaccination programs are about to start and also gentherapy protocols.

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Genetic counselling for cancer predisposition

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The availability of diagnostic molecular testing for inherited cancer calls for health care professionals to identify families at risk and to advise them of surveillance and prevention strategies. The demand for specialized Cancer Genetics Services is increasing rapidly because of heightened public awareness of genetic aspects of cancer susceptibilty and because of requests from primary care physicians for risk assessment and recommendations for appropriate management options for families with an inherited cancer susceptibility. However, the complex medical, ethical, legal and psychosocial issues brought by our ability to test healthy individuals for cancer predispositions and the rapid pace of new research findings pose great challenges to the medical community. The setup and provision of Cancer Genetics Clinics and presymptomatic Molecular Testing Services for inherited cancer as well as the education and training of health professionals involved in the provision of Cancer Genetics Services across Europe will be reviewed and issues such as how these services may best be organized and evaluated as well as the question at which level of care families at slightly, intermediately and highly elevated risk for cancer should be managed will be discussed.

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Recording of morbidity

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All modalities employed for the treatment of the patient with cancer are associated with a risk of side effects but with most these become evident during or soon after treatment. Radiotherapy, however, differs in that the dose-limiting side effects commonly occur many months and sometimes many years after the treatment. The recording of the morbidity of treatment presents a special challenge for the

Radiation Oncologist.

The description of individual cases prevailed in the first half of this 20th-century but as we moved into the world of the randomised controlled clinical trial there was a need for a systematic approach which could be applied on an international basis. The WHO (1979) was essentially developed for the recording of the morbidity associated with cytotoxic chemotherapy but the RTOG/EORTC system for the acute and late morbidity of radiotherapy soon followed. The Franco-Italian Glossary proved valuable for the recording of morbidity due to both radiotherapy and surgery in gynaecological cancer.

All stagings were a combination of symptoms, signs, investigations and treatment and the European Dictionary was introduced in 1989 to capture the elements making up morbidity. In 1995 the LENT/SOMA was introduced as an advance on the original RTOG/EORTC in that it gave a more detailed description of the morbidity of radiotherapy with some separation of the elements making up that morbidity. In the United States the CTC version 1 (1984) built upon the original WHO was updated to version 2 in 1998 covering the sites of morbidity in much greater detail and an attempt was made to include the morbidity of all cancer treatment. In 2003 the CTC version 3 included over 500 criteria to cover all the morbidity of cancer treatment. The exact value of this system and the preceding ones needs careful consideration.

As we enter the 21st century we are aware that patients and their families have become more critical of cancer care demanding not only cure but freedom from side effects. In order to deal with this we must have accurate data as to the incidence. The complex systems required for careful assessment of morbidity in randomised controlled trials are quite unsuitable for the assessment of morbidity in the general care of all patients with cancer. Until recently this has been given very little attention now however systems are under study which may well satisfy this need.

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Nuclear medicine in the diagnosis and treatment of paediatric tumours

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In recent years the contribution of nuclear medicine has been of increasing interest to paediatric oncology, in particular in imaging for diagnosis, staging and follow-up, in quantitative function analysis of organs at risk during oncological therapy, as well as in radionuclide therapy.

For tumour imaging a great number of tumour-seeking radiopharmaceuticals are available, exploiting various metabolic and biological properties of individual tumours; several of these agents can also be applied for radionuclide therapy. More recent tracers allow the characterization of tumours, highlighting features like hormone receptors, hypoxia, MDR and apoptosis. New techniques in paediatric oncology include PET and probe-guided surgery. A summary of applications and major indications will be presented.

Osteosarcoma/EWING's sarcoma. In differentiated osteosarcoma bone scintigraphy and SPECT using ^{99m}Tc-diphosphonate, targeting the tumour-produced osteoid, may visualize not only the primary bone tumour and skeletal metastases, but also the extraosseous metastases. For preoperative therapy and palliation of metastases beta-emitting bone-seeking agents, such as ^{89}Sr-chloride, ^{186}Re-HEDP and ^{153}Sm-EDTMP, are available.

Lymphoma. ^{67}Ga-citrate has been used for decades in the detection, staging and follow up of lymphoma, as well as for early recognition of response to therapy. ^{201}Tl-chloride scintigraphy + SPECT and PET using ^{18}F-deoxyglucose can also be used for this purpose. ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are associated with p-glycoprotein, playing a role in multidrug resistance. In adults with recurrent non Hodgkin lymphoma treatment with ^{131}I- or ^{90}Y labelled anti-CD20 antibodies is highly effective.

Thyroid carcinoma. ^{201}Tl-chloride scintigraphy together with thyroglobulin assays has become a reliable alternative to the use of ^{131}I-iodide in the follow-up of differentiated thyroid carcinoma; procedure and radiation dose to the child compare favourably with that of ^{131}I. Iodine-131 maintains its role in radionuclide therapy of thyroid carcinoma. When children become involved in the family screening of MEN 2 syndromes, a variety of tracers can be used to demonstrate medullary thyroid carcinoma:

Neuroblastoma. Because of its high sensitivity and specificity, scintigraphy using ^{123}I- or ^{131}I-metaiodobenzylguanidine (MIBG) has established its role in the diagnosis, staging and follow-up of neuroblastoma. ^{131}I-MIBG is used for the treatment of this condition. Alternatively, specific targeting may be achieved using radiolabelled peptides (e.g. ^{111}In-pentetreotide) or monoclonal antibodies (e.g. 3F8, UJ13A, BW575/9, ch14.18 and chCE7). PET using ^{18}F-deoxyglucose (FDG) and ^{11}C-hydroxyephedrin (HED) is used to image neuroblastoma and ^{124}I-MIBG and -3F8 antibodies for dosimetry prior to therapy.

Rhabdomyosarcoma. Aspecific tracers, e.g. ^{67}Ga-citrate, ^{201}Tl-chloride and ^{18}F-deoxyglucose, can be used to image rhabdomyosarcoma. An example of specific targeting of rhabdomyosarcoma is radioimmunoscintigraphy using ^{111}In antimyosin Fab fragments, but these are no longer commercially available.

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Will oral drug replace IV treatment?

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Unlike most therapeutic areas where oral treatment is standard, in oncology most drugs are given intravenously. Encouraging clinical trial results indicate that for first time many of the orals anti-cancer drugs in development are better drugs rather than pale imitations of i.v. treatments. The oral route is appropriate for schedule dependent cytotoxics e.g. fluoropyrimidines as well as novel agents including signal transduction inhibitors and anti-angiogenic agents in order to achieve prolonged exposure.

Although more than 20 cytotoxics are available orally, many such as cyclophosphamide, etoposide and topotecan are also given i.v. Currently, probably the widest use of oral chemotherapy is 6-mercaptopurine, methotrexate and busulphan in leukaemias and lymphoma. Temozolamide (for glioma, astrocytoma and melanoma) and idarubicin (principally for leukaemia) are also well established but again have had limited impact as these are not the commonest cancers. 5-fluorouracil (5-FU) is, however, widely used and oral alternatives have been developed including pro-drugs that are absorbed unchanged (capecitabine, tegafur), the addition of inhibitors of the enzyme DPD that catabolizes 5-FU (uracil, eniluracil), or a combination of the two (UFT, S1, emitefur). With capecitabine now approved in

breast and colorectal cancer, the profile of oral chemotherapy is set to rise. Oral formulations of other cytotoxics, such as the taxanes, are also in development.

Potentially even more important in the future will be novel agents targeted to intra-cellular signalling pathways such as protein kinases. Several are being developed as oral therapies with imatinib and iressa leading the way. Imatinib, which inhibits the c-abl and c-kit tyrosine kinases, has excellent oral bioavailability and striking activity in CML and G.I. stromal tumours. Iressa is an oral anilinoquinazoline inhibitor of EGFR tyrosine kinase activity given once daily by mouth with activity in non-small cell lung cancer. Both iressa and tarceva (an oral quinazoline EGFR tyrosine kinase inhibitor also active in non-small cell lung cancer) cause a reversible acneiform rash. The same rash is seen with C225, the intravenously administered monoclonal antibody EGFR inhibitor emphasizing that route of administration alone will not avoid a "class effect" toxicity.

Although oral treatment is set to increase, concerns remain regarding compliance, absorption and variable pharmacokinetics as well as re-imbursement in some countries. The overwhelming majority of patients prefer oral chemotherapy (>80%) because of its greater convenience, avoidance of venepunctures and the greater sense of "control" over their treatment. Clinicians often question whether patients will take tablets reliably, but evidence for non-compliance is conflicting. Likewise, concerns over the consistency of bioavailability can often be overcome by improved formulation and drug delivery. There may also be an assumption amongst oncologists that i.v. administration is inherently more effective than oral treatment despite experience showing that in women with breast cancer responses are more durable with oral endocrine therapy than i.v. chemotherapy. Indeed, we must remember that anti-cancer drugs potentially toxic irrespective of the route of administration and must be carefully supervised by the oncology team. It is especially important to educate patients taking oral drugs, as well as their G.P., practice nurse and pharmacist, to recognise side-effects so that treatment can be interrupted where appropriate.

The development of oral chemotherapy is not straightforward. Some patient populations such as those who have undergone upper G.I. tract or head and neck surgery and children may not be good candidates for oral treatment. Factors such as food, age and concomitant medications may all influence systemic bioavialability. Dosing issues also differ for oral drugs where there is a strong argument for "flat dosing" irrespective of body surface area. Development of an oral drug may, therefore, be more complex than for i.v. cytotoxics and require more detailed pharmacokinetic studies and evaluation of potential interactions. These problems have, however, been overcome in other therapeutic areas and are now being addressed in oncology.

Funding of heath-care is an issue everywhere, although the specific concerns vary from country to country. Assuming equivalent efficacy, we can expect that patients would choose oral chemotherapy but will physicians be able and willing to follow their lead? A particular problem is that in some countries oral treatment may generate less income for the hospital and the doctor. Differences in reimbursement and physician remuneration between Europe and the United States mean that American oncologists may be less enthusiastic about oral chemotherapy. Oral treatment will reduce the number of in-patient and out-patient hospital visits with their associated medical and nursing, administrative costs; avoid the cost of disposables (e.g. infusion equipment, pumps) and decrease the pharmacy workload. Currently, chemotherapy costs account for about 5% of the direct cost of cancer care so it should be possible to set increased drug costs against the substantial savings that will be made elsewhere. Drug budgets are, however, easily identified and this process will be easier in some countries than in others.

Plenary Session

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Cancer clinical trials - the key to improving outcome

I. Tannock. *Princess Margaret Hospital and University of Toronto, Dept of Medical Oncology, Toronto, Canada*

Improvements in outcome for cancer patients must be built on evidence and not on opinion (even expert opinion). Various agencies have established guidelines for treatment of common types and stages of cancer that are based on a hierarchy of clinical trials, with large randomised trials and meta-analyses providing highest levels of evidence. However, in assembling the evidence, it is important to evaluate (i) the quality of clinical trials, (ii) whether patients recruited to the trials were representative of those with similar type and stage of cancer, and (iii) whether there was bias in selection of trials.

A systematic method for evaluating the quality (or "internal validity") of a clinical trial is to ask the following:

1. Does the study address an important question?
2. Is the design of the study appropriate? (i.e. randomised design and blinding if feasible, sample size and statistical issues; explicit definition of primary endpoint)
3. Are the endpoints of the study appropriate – do they reflect benefit to patients (overall survival, quality of life) or merely biological activity (tumour response)?
4. Do the analysis and report of the study truly reflect its results?

Trials should also be examined for consistency with clinical experience and with the results of other relevant trials ("external validity"). Important trials should always be repeated before their results are used to change the standard of care.

Patients are often selected for inclusion in clinical trials (e.g. by high performance status) and it is important to ask whether the results of the trial can be generalised to other cancer patients.

We have shown that even large randomised cancer trials are subject to publication bias whereby those with negative results are delayed in publication in comparison to positive trials, or are not published at all. This can cause serious bias in compiling evidence; it is imperative to seek evidence of publication bias when compiling evidence.

Overall, improving outcome for cancer patients requires that the right treatment be given, that it be given well, and that it be given with compassion and support. Clinical trials provide the key to the first of these requirements, and treatment of patients within the context of a clinical trial may help to ensure the second, and contribute to the third. It is perhaps for these reasons that patients recruited to clinical trials may have better outcome as compared to similar patients who are not included in clinical trials.

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The usefulness of meta-analysis in decision making

M. Parmar. *MRC Clinical Trials Unit, Cancer Division, London, United Kingdom*

In all the important decisions we make in life information and evidence is key. In medicine, the randomised controlled trial is universally acknowledged as providing key unbiased information which is the foundation for evidence-based medicine. High quality meta-analyses go a step further than the individual trial by trying to obtain as complete a picture as possible by summarising the results of *all* the relevant randomised trials. In this presentation we discuss how meta-analyses have reliably shown which treatments are effective, which are not and also identified some, which have been positively harmful. Without these meta-analyses we argue that we would still be unsure as to the value of a number of these treatments. Nevertheless, it is unrealistic to expect that an individual trial or meta-analysis will give "prescriptions" on how each individual patient should be treated, rather it gives guidance on how populations of patients with a certain disease should be treated. Thus, a useful way of considering the interpretation of a meta-analysis showing a positive result for a new treatment is that it should change the stance of the doctor (and patient), from one of "is there any good reason why I should use this new treatment in this patient?" to "is there a good reason why I should not use this new treatment?". Meta-analyses are also critical for helping us decide on the direction and focus for future research. At its simplest level a high quality meta-analysis summarises what has been done and what the outcomes were. If we do not have this information when designing a new trial, we argue that we are in danger of undertaking inappropriate and unethical research. Finally, we argue that unless we plan better for the future, meta-analyses will not be as informative as they have been in the past.